

FULL PROTOCOL TITLE

Norepinephrine-targeted therapy for Action Control in Parkinson Disease

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SYNOPSIS

Study Title

Norepinephrine-targeted therapy for Action Control in Parkinson Disease

Objectives

Primary Objective: To assess the safety and tolerability of droxidopa combined with carbidopa in a Parkinson disease cohort

Secondary Objectives:

- a) To determine the optimal dosing regimen for combined droxidopa and carbidopa therapy in this patient population
- b) To explore the effects of central norepinephrine repletion on action control in Parkinson's disease patients

Design and Outcomes

This is an 11-week, prospective, open label, safety and tolerability study evaluating high doses of carbidopa with concomitant droxidopa therapy in PD. The study will consist of an initial screening and baseline period, followed by a one week treatment period on carbidopa alone. This will then be followed by a 3 week treatment period on droxidopa and carbidopa, followed by a one month washout.

Patients will be enrolled into the study at the Screening visit if they meet the inclusion criteria (see Section 4.1). UPDRS scales will be performed by a trained site rater in order to determine PD subtype. Those who are classified as PIGD based on UPDRS motor score will be enrolled and will undergo cognitive and gait assessments at the Baseline Visit. They will then begin carbidopa therapy as described above.

Patients will return to the clinic at Week 3 for repeat cognitive and gait assessments. Droxidopa titration will be initiated at this point. Patients will then return at Weeks 5 and 7 for repeat testing. Droxidopa will then be tapered and patients will return for one final visit after a one month washout period.

Patients who withdraw from the study before completion of the 11-week evaluation period will have final assessments performed at their final visit.

Baseline PD medications should remain unchanged throughout the study. The total dose of carbidopa, from baseline medications and supplemental dosing, should remain constant.

Interventions and Duration

The study drug is Northera (droxidopa), to be given along with carbidopa, a dopa decarboxylase inhibitor.

Following the Screening/Baseline visit, patients will be started on carbidopa alone. Those who are not already taking a carbidopa-containing medication (i.e. carbidopa-levodopa) will be started on 200mg BID. For those who are on a carbidopa-containing medication, the necessary supplemental dose will be calculated in order to increase their total dose to 200mg BID, or a total of 400mg per day. This dosing regimen will continued for the duration of the study in order to maximize the central bioavailability of droxidopa and to limit peripheral effects.

After one week patients will return for Visit 1 and will have repeat cognitive testing to ensure all measures remain stable. Droxidopa titration will then be initiated. Droxidopa will be supplied in 100mg tablets. Dosing will start at 100mg BID and will be increased by 100mg BID every day for 6 days, up to a maximum of 600mg BID. If at any point patients develop adverse effects, the dose will be decreased back to the maximum tolerated dose.

Treatment with droxidopa and carbidopa at the maximum tolerated dose will be continued for an additional 3 weeks after the titration, followed by a one month washout period.

Subjects will be monitored for adverse events and safety outcomes throughout the study period. Cognitive testing and gait assessments will occur at weeks 3, 5, 7, and 11.

Sample Size and Population

Fifteen adult idiopathic Parkinson disease (PD) patients identified as postural instability-gait difficulty (PIGD subtype) will be enrolled.

1 STUDY OBJECTIVES

Primary Objective

Primary Objective: To assess the safety and tolerability of droxidopa combined with carbidopa in a Parkinson disease cohort.

Primary Hypothesis: Combination droxidopa and carbidopa therapy will be safe and tolerable (defined as adverse events leading to discontinuation in less than or equal to 20% of subjects) in this cohort of Parkinson disease patients.

Secondary Objectives

Secondary Objectives:

- a) To determine the optimal dosing regimen for combined droxidopa and carbidopa therapy in this patient population.
- b) To explore the effects of central norepinephrine repletion on action control in Parkinson's disease patients.

2 BACKGROUND

Rationale

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 1 million people in the United States. PD causes a variety of disabling symptoms, which impact movement as well as cognition. Many of the symptoms of PD can be attributed to loss of dopaminergic neurons, although other neurotransmitter systems are affected as well. Historically, much of the treatment of PD has focused on dopamine repletion. This can be effective for some of the symptoms of PD, such as rigidity and bradykinesia, although it is quite ineffective for others, including gait and cognitive dysfunction. One possible reason for this may be non-dopamine mediated degeneration affecting other neurotransmitter systems including acetylcholine and norepinephrine. Norepinephrine, in particular, is measurably deficient in PD patients and is critical for a number of processes which are affected by PD, including attention and action control. Deficits in action control lead to an inability to inhibit impulsive actions, which can result in a variety of manifestations, including gait dysfunction and falls. These symptoms can be disabling and are notoriously resistant to dopamine replacement therapy.

Previously we have not been able to directly investigate the effects of central norepinephrine repletion in PD, but the recent approval of droxidopa, a norepinephrine precursor, presents a novel opportunity to address this question. The primary goal of this small, single-arm study will be to assess the safety and tolerability of droxidopa combined with carbidopa, a DOPA decarboxylase inhibitor which allows droxidopa to cross the blood-brain barrier. We will also include several exploratory measures to investigate the effects of centrally-targeted droxidopa therapy on action control in PD patients, using

several well-validated cognitive assessments as well as a computerized gait assessment. We will also include measures of autonomic function and imaging data.

Our overarching hypothesis is that norepinephrine targeted therapy will be well-tolerated in our PD cohort and will have the potential to improve motor control symptoms characterized by action impulsivity, motor inhibition, and reaction time.

Noradrenergic neurons are located in the locus coeruleus (LC) and have widespread projections to the cortex, basal forebrain, limbic system, thalamus, and cerebellum, including key prefrontal areas involved in inhibitory action control. It has long been recognized that locus coeruleus neurons degenerate in PD, and Lewy body pathology is found in the LC at autopsy in PD patients (1). In fact, studies have shown that degeneration in the LC is comparable to and may even precede the degeneration of dopaminergic neurons in the substantia nigra (2). Furthermore, the cerebrospinal fluid of PD patients contains measurably lower levels of norepinephrine (3) as well as dopamine beta-hydroxylase, the key enzyme for norepinephrine synthesis (4).

Norepinephrine (NE) is essential for a wide range of functions in the nervous system, and its deficiency in PD may underlie a number of symptoms in this disease, particularly those which tend to respond poorly to dopaminergic therapy. One critical process in which NE has been shown to play a central role is action control (5,6). This refers to the ability to select and perform an appropriate action while effectively inhibiting inappropriate ones. Impaired action control is a well-recognized feature of PD which often emerges relatively early in the disease process and can lead to significant disability. Previous work from our lab has shown that impairments in action control are associated with greater postural instability, fall risk, and a marker of worsening disease severity in PD (7,8). The network underlying action control relies on a well-described motor-inhibitory circuit, which includes the dorsal lateral prefrontal cortex, basal ganglia, and subthalamic nucleus. The LC projects directly to this circuit and its noradrenergic inputs modulate its activity. Therefore, NE deficiency in PD is likely a major factor in the impaired inhibitory control seen in these patients. As impairments in action control are closely linked to gait dysfunction in PD, correcting this NE deficiency would be expected to have a direct influence on gait as well.

Several previous studies have investigated the effects of norepinephrine on gait. Animal studies have shown that mice deficient in NE show significantly greater motor impairment when exposed to MPTP, a toxin which creates a PD phenotype, than do control mice (9). In addition, a few small studies in PD patients have found that methylphenidate, a norepinephrine and dopamine reuptake inhibitor, may have beneficial effects on freezing and gait (10,11,12). A review by Devos et al in 2013 suggested that methylphenidate may improve freezing of gait as well as apathy (13). Most of these were short term investigations, but another study by Devos et al in 2007 evaluated the use of high dose methylphenidate over a 3 month period in a group of 17 patients and found improvements in gait and motor symptoms in the absence of levodopa, with enhanced improvement on levodopa (14). The authors suggest that interactions between the norepinephrine and dopamine systems as well as increased norepinephrine in frontal networks could be responsible for these effects.

As previously referenced, some studies from Japan in the 1980-90's have suggested that treatment with L-threo-34-dihydroxyphenylserine (L-DOPS) improves freezing of gait (15,16). Finally, during the

approval process for droxidopa in the US, a decreased rate of falls was reported in PD patients treated with droxidopa vs. placebo in one preliminary study (17).

The possibility that norepinephrine replacement may have a positive impact on action control and gait in PD is promising but remains to be proven. With the approval of droxidopa in the U.S., we now have a unique opportunity to study the central effects of norepinephrine and to directly assess its role in PD. The primary goal of the proposed study is to examine the safety and tolerability of droxidopa combined with carbidopa in a cohort of PD patients. Secondary measures will include several well-studied cognitive tasks to assess the effects of centrally-targeted norepinephrine on action control.

Supporting Data

Northera (droxidopa) is indicated for the treatment of orthostatic dizziness or lightheadedness in adult patients with symptomatic neurogenic orthostatic hypotension caused by Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy (refer to Appendix A for prescribing information).

The safety of Northera was evaluated in two 1- to 2-week placebo-controlled studies (Studies 301 and 302), one 8-week placebo-controlled study (Study 306), and two long-term, open label extension studies (Studies 303 and 304). The placebo-controlled studies included a total of 485 patients with Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy. 245 patients received Northera and 240 received placebo. The long-term, open-label extension studies included a total of 422 patients who were treated with Northera for a mean duration of approximately one year.

In the placebo-controlled trials, the most commonly observed adverse reactions (occurring in greater than 5% of patients in the Northera group and with at least a 3% greater incidence than in the placebo group) were headache, dizziness, nausea, and hypertension. Hypertension and nausea were the most common adverse reactions leading to discontinuation of Northera. In the long-term, open-label extension studies, the most commonly reported adverse events were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).

The efficacy of Northera in the treatment of symptomatic neurogenic orthostatic hypotension (NOH) was evaluated in clinical studies 301 and 306B.

Study 306B enrolled 171 patients with symptomatic NOH and PD. 147 patients were included in the efficacy analysis. This was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study which consisted of an initial dose titration period of up to 2 weeks, followed by an 8-week treatment period. Patients were randomized to receive placebo or 100 to 600mg of Northera three times a day during the titration period and were continued on a stable dose during the treatment period. Efficacy was measured by the change in dizziness score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") from baseline to Week 1 in patients who had completed titration and 1 week of maintenance therapy. The baseline dizziness score was the same in both groups prior to titration. At Week 1 there was a statistically significant decrease in dizziness score in the Northera treatment group vs. placebo ($p=0.028$), but this effect did not persist beyond Week 1. The lowest systolic

blood pressure after 3 minutes of standing also increased more in patients receiving Northera than placebo ($p=0.032$).

Study 301 enrolled a total of 122 patients with symptomatic NOH due to Parkinson's disease ($n=60$), pure autonomic failure ($n=36$), or multiple system atrophy ($n=26$). This was a multi-center, multinational, double-blind, randomized, placebo-controlled, parallel-group study which consisted of an initial open-label dose titration period, a 7-day washout period, and a randomized double-blind 7-day treatment period. Only patients who were identified as "responders" during the titration period (improvement by at least 1 point on the dizziness score, as well as an increase in standing systolic blood pressure by at least 10 mm Hg) were included in the randomized treatment phase. A statistically significant treatment effect was not found on the Orthostatic Hypotension Questionnaire ($p=0.19$), but there was a significant decrease in dizziness score after Week 1 of treatment in the Northera treatment group vs. placebo ($p=0.06$).

Two additional studies evaluated the effectiveness of Northera beyond 2 weeks. Study 302 was a placebo-controlled, 2-week randomized study of 101 patients with symptomatic NOH. Study 303 was an extension of studies 301 and 302 in which 75 patients were continued on maintenance dose Northera for 3 months, followed by a 2-week randomized withdrawal phase. Neither of these studies showed a statistically significant difference in the efficacy of Northera as compared with placebo beyond 2 weeks.

A few previous studies have examined the effects of Northera on gait, although this is an area which warrants further investigation. Study 306A compared scores on the Orthostatic Hypotension Questionnaire (OHQ) as well as dizziness/lightheadedness score and patient-reported falls between a group of 24 patients treated with droxidopa and a group of 27 patients treated with placebo. In this study no significant difference was found in OHQ score, but the droxidopa group reported a 50% lower rate of falls ($p=0.04$) and fall-related injuries. In addition, several studies from Japan in the 1980-90's have suggested that treatment with L-threo-34-dihydroxyphenylserine (L-DOPS) improves freezing of gait (15,16).

Known and Potential Risks and Benefits for Droxidopa

The most commonly observed adverse reactions in the placebo-controlled safety and efficacy trials described above were headache, dizziness, nausea, and hypertension. Longer term open-label studies also reported falls, urinary tract infections, headache, syncope, and dizziness.

Northera carries four specific warnings on its label. The first states that Northera may cause or exacerbate supine hypertension in patients with symptomatic NOH. Patients are advised to elevate the head of the bed while resting or sleeping, and to monitor blood pressure in both the supine position and the head elevated position. Northera should be reduced or discontinued if supine hypertension persists despite these measures.

The second warning pertains to a symptom complex of hyperpyrexia and confusion resembling neuroleptic malignant syndrome. Cases of this syndrome have been reported in Japan during post-marketing surveillance. Symptoms may include fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes.

The third warning listed on the Northera label states that there is a risk of exacerbating existing ischemic heart disease, arrhythmias, and congestive heart failure.

The final warning reports a risk of allergic reaction in patients with sensitivity to tartrazine (FD&C Yellow No. 5). This is rare but frequently seen in patients who also have aspirin hypersensitivity.

Northera is listed as pregnancy category C. There are no adequate and well-controlled trials of this medication in pregnant women. Animal studies have suggested increased incidences of lower body weight and occurrence of undulant rib in fat fetuses, although these spontaneously reversed after birth. Shortening of the gestation period was also noted at high doses (600mg/kg/day). Low incidences of renal lesions were also observed in female rats treated with droxidopa during the period of fetal organogenesis.

Nursing is contraindicated with Northera. Droxidopa is excreted in breast milk in rats and has been found to be associated with reduced weight gain and reduced survival in offspring.

Additional information regarding the risks and benefits of droxidopa treatment may be found in the current Northera prescribing information.

Known and Potential Risks and Benefits for Carbidopa

Carbidopa (Lodosyn) is an inhibitor of aromatic amino acid decarboxylation. It is indicated for use with levodopa in the treatment of Parkinson's disease in order to inhibit the peripheral metabolism of levodopa, thus allowing more levodopa to enter the central nervous system and reducing the rates of nausea and vomiting.

Carbidopa alone has not been associated with any adverse effects. When administered in combination with levodopa, the most common adverse reactions include dyskinesias and nausea. Other reported adverse reactions include delusions, hallucinations, impulse control behaviors, and depression. Convulsions have also occurred although a causal relationship has not been established.

Additional warnings listed for patients taking carbidopa-levodopa combination products include a risk of somnolence with occasional episodes of suddenly falling asleep, as well as sporadic cases of a symptom complex resembling neuroleptic malignant syndrome. Some patients taking carbidopa-levodopa products have reported suddenly falling asleep while engaged in daily activities, sometimes without prior warning. Some of these cases have occurred during driving, resulting in motor vehicle accidents. Patients should be screened for pre-existing drowsiness as well as other factors that may increase the risk of somnolence, such as sedating medications and sleep disorders. Neuroleptic malignant syndrome has been reported in association with dose reductions or discontinuation of dopaminergic agents including carbidopa-levodopa combination products. Patients should be monitored closely for any symptoms resembling this syndrome during dose changes or withdrawal of this medication.

Additional information regarding the risks and benefits of droxidopa treatment may be found in the current Lodosyn prescribing information.

Known and Potential Risks and Benefits for Droxidopa Combined with Carbidopa

As Northra is a synthetic amino acid analog that is metabolized to norepinephrine by dopa-decarboxylase, co-administration along with a dopa-decarboxylase inhibitor such as carbidopa would be expected to inhibit its peripheral metabolism, reducing peripheral effects such as hypertension and increasing its central activity. While there have not yet been any studies to our knowledge specifically investigating the effects of combining droxidopa with carbidopa, many of the patients enrolled in the safety and efficacy studies for Northra were exposed to both concomitantly, given the very common usage of carbidopa-levodopa in Parkinson's disease. 88% of the 171 patients enrolled in Study 306B and 45% of the 122 patients in Study 301 were taking a dopa-decarboxylase inhibitor, representing a total of 210 patients. No difference in adverse reactions was reported in these patients as compared with the rest of the study population.

Administering droxidopa along with carbidopa would be expected to be associated with a reduced risk of hypertension as compared with droxidopa alone, as this is a peripheral effect resulting from arterial and venous vasoconstriction induced directly by norepinephrine. Therefore, inhibiting the peripheral metabolism of droxidopa will limit these effects and increase the central activity of norepinephrine. In the studies performed thus far, no additional adverse events have been reported in those patients treated with droxidopa along with carbidopa as compared with droxidopa alone, although further investigation is warranted. The proposed study will therefore provide valuable clinical experience to better elucidate the effects of centrally-targeted norepinephrine.

Selection of Drugs and Dosages

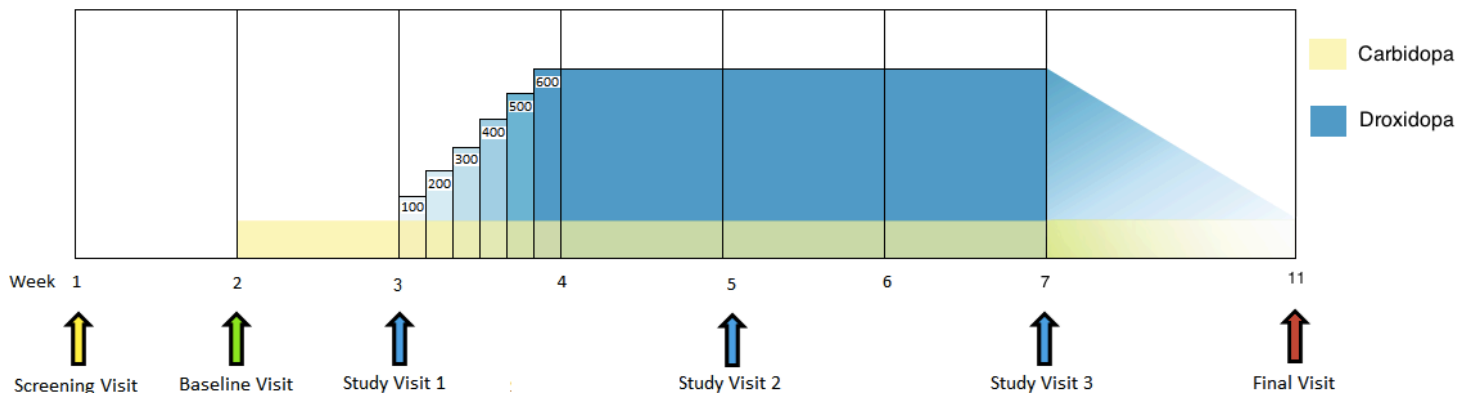
Northra is available in 100mg, 200mg, and 300mg capsules. The recommended starting dose is 100mg three times daily, with the last dose at least 3 hours prior to bedtime. The dosing is titrated to symptomatic response in increments of 100mg three times daily every 24 to 48 hours. The maximum dose is 600mg three times daily.

Carbidopa is available in 25mg tablets. When given along with levodopa it is typically dosed in a carbidopa to levodopa ratio ranging from 1:10 to 1:4, depending on therapeutic response. The typical recommended total daily dose of carbidopa is 75mg to 200mg, although studies have shown that doses up to 450mg/day are well-tolerated and may further improve the response to levodopa (Brod et al, 2013). No cases of carbidopa overdose have been reported.

3 STUDY DESIGN

This is an 11-week, prospective, open label, safety and tolerability study evaluating high doses of carbidopa with concomitant droxidopa therapy in PD. The study consists of an initial screening and baseline period, followed by a one week treatment period on carbidopa alone. This will then be followed by a 3 week treatment period on droxidopa and carbidopa, followed by a one month washout.

Each subject will participate in six visits over the course of this trial, as summarized in the figure below.



Patients will be enrolled into the study at the Screening visit if they meet the inclusion criteria outlined below. UPDRS scales will be performed by a trained site rater in order to determine PD subtype. Those who are classified as PIGD based on UPDRS motor score will be enrolled and will undergo cognitive and gait assessments at the Baseline Visit.

After the Baseline Visit, each subject will be started on a stable dose of carbidopa to reach a total of 200mg BID. This will be continued for the next week until Study Visit 1. At this visit, repeat cognitive assessments (Stop-Signal, Simon, and Attentional blink tasks) and a gait assessment will be performed. Orthostatic vital signs will also be measured.

Each subject will then undergo titration of droxidopa to the maximum tolerated dose with a target of 600mg BID. Dosing will start at 100mg BID and will be increased by 100mg BID every day for 6 days, up to a maximum of 600mg BID. If at any point patients develop adverse effects, the dose will be decreased back to the maximum tolerated dose. 200mg of carbidopa will also be given with each dose of droxidopa, for a total daily dose of 400mg, to maximize central bioavailability and limit peripheral effects.

Study Visit 2 will take place one week after each patient is stabilized on the maximum tolerated dose of droxidopa (goal 600mg BID). Study Visit 3 will take place two weeks after Study Visit 2, after patients have been on maintenance therapy for a total of 3 weeks. Each of these visits will consist of the same assessments as Study Visit 1, including cognitive and gait assessments and orthostatic vital signs.

After Study Visit 3 has been completed, each subject will be tapered off droxidopa and carbidopa. The final visit will take place after a one month washout period and will again include cognitive testing and a gait assessment.

4 SELECTION AND ENROLLMENT OF SUBJECTS

Inclusion Criteria

Patients will be included in the study if all of the following criteria are met:

- a. Nondemented man or woman 18 years of age or older with idiopathic PD based on the UK Parkinson Disease Society Brain Bank Clinical Diagnostic Criteria (refer to Appendix C for the criteria)
- b. Unified Parkinson Disease Rating Scale (UPDRS) motor scores OFF medication consistent with PIGD subtype
- c. Symptoms of freezing or falls
- d. Able to walk at least 10 meters
- e. Medically stable outpatient, based on the investigator's judgment
- f. The patient must be willing and able to give written informed consent prior to performing any study procedures.

Exclusion Criteria

Patients are excluded from participating in this study if one or more of the following criteria are met:

- a. Score of 21 or lower on MOCA
- b. Sustained supine hypertension greater than or equal to 180 mmHg systolic or 110mmHg diastolic, or have these measurements at their Baseline Visit (Visit 2). Sustained is defined as measurements persistently greater at 2 separate measurements at least 10 minutes apart with the subject supine and at rest for at least 5 minutes.
- c. Concomitant use of vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine. Concomitant use of other noradrenergic medications, such as serotonin-norepinephrine reuptake inhibitors (SNRI's) is also contraindicated. Patients must stop taking these drugs at least 2 days or 5 half-lives (whichever is longer) prior to their baseline visit and throughout the duration of the study.
- d. Diagnosis of hypertension that requires treatment with antihypertensive medications (short-acting antihypertensives to treat nocturnal supine hypertension are allowed in this study)
- e. Women of childbearing potential
- f. Any significant uncontrolled cardiac arrhythmia
- g. History of myocardial infarction, within the past 2 years
- h. Current unstable angina
- i. Congestive heart failure (NYHA Class 3 or 4)
- j. History of cancer within the past 2 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma or cervical cancer in situ
- k. History of stroke
- l. Gastrointestinal condition that may affect the absorption of study drug (e.g., ulcerative colitis, gastric bypass)

- m. Musculoskeletal disorders such as severe arthritis, post knee surgery, hip surgery, or any other condition that the investigators determine may impair assessment of gait
- n. History of myocardial infarction, uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or stroke
- o. Untreated closed angle glaucoma
- p. Musculoskeletal or other disorders that may impair assessment of gait
- q. Any major surgical procedure within 30 days prior to the Baseline visit
- r. Previously treated with droxidopa within 30 days prior to the Baseline visit
- s. Currently receiving any other investigational drug or have received an investigational drug within 60 days prior to the Baseline visit
- t. Known or suspected alcohol or substance abuse within the past 12 months (DSM-IV definition of alcohol or substance abuse)
- u. Any condition or laboratory test result, which in the Investigator's judgment, might result in an increased risk to the patient, or would affect their participation in the study.

Study Enrollment Procedures

Prospective participants will be selected from the existing patient population of the Movement Disorders Clinic at Vanderbilt University Medical Center. They will be selected during a regular standard of care visit.

At a standard of care visit, patients will be screened by their respective physicians. Those who are identified as being able to participate will be referred over to the investigator. The investigator will confirm eligibility of participants using the Inclusion/Exclusion Criteria. Each patient must be willing and able to give written informed consent prior to performing any study procedures. An informed consent form will be approved by the Vanderbilt IRB. The principal investigator will explain the consent form to the potential participant, including the rationale for the study, the procedures involved, the duration of participation, and the potential risks and benefits involved. Privacy will be provided per HIPAA and standard of care procedures. If the subject chooses to proceed with the study, the informed consent form will then be signed.

A screening log will be maintained in order to document how each subject learned about the trial, reasons for ineligibility, and any reasons for nonparticipation of eligible subjects. This information will be collected and stored confidentially and will be utilized in order to enhance recruitment efforts.

5 STUDY INTERVENTIONS

Interventions, Administration, and Duration

The study drug is Northera (droxidopa), to be given along with carbidopa, a dopa decarboxylase inhibitor.

Following the Screening/Baseline visit, patients will be started on carbidopa alone. Those who are not already taking a carbidopa-containing medication (i.e. carbidopa-levodopa) will be started on 200mg BID. For those who are on a carbidopa-containing medication, the necessary supplemental dose will be

calculated in order to increase their total dose to 200mg BID, or a total of 400mg per day. This dosing regimen will continued for the duration of the study in order to maximize the central bioavailability of droxidopa and to limit peripheral effects.

After one week patients will return for Visit 1 and will have repeat cognitive testing to ensure all measures remain stable. Droxidopa titration will then be initiated. Droxidopa will be supplied in 100mg tablets. Dosing will start at 100mg BID and will be increased by 100mg BID every day for 6 days, up to a maximum of 600mg BID. If at any point patients develop adverse effects, the dose will be decreased back to the maximum tolerated dose.

Treatment with droxidopa and carbidopa at the maximum tolerated dose will be continued for an additional 3 weeks after the titration, followed by a washout period. If a dose is missed, the next dose should be taken at the usual time on the following day. The patient should not double-up the dose of the study drug.

Study drug will be packaged in bottles and provided to the patients to be administered at home. The study drug will be dispensed to the patient at the study center by a person authorized by the study investigator at each scheduled visit.

Handling of Study Interventions

Lundbeck is responsible for the manufacturing of the droxidopa capsules.

During the titration phase, patients will be started on 100mg twice daily. The dose will be increased in increments of 100mg BID each day to a maximum dose of 600mg BID.

Packaging, labeling, and distribution of the study drug and supplies will be performed by Lundbeck. Each bottle will contain 90 tablets.

Health & Wellness Compounding Pharmacy is responsible for the manufacturing of the carbidopa capsules. Carbidopa will be supplied in 25mg capsules. Patients who are not already taking a carbidopa-containing medication (i.e. carbidopa-levodopa) will be started on 200mg of carbidopa twice daily. For those who are on a carbidopa-containing medication, the necessary supplemental dose will be calculated in order to increase their total dose to 200mg BID, or a total of 400mg per day.

The study drugs will be packaged and shipped in appropriate storage boxes. Each study drug shipment will include a packing slip, listing the contents of the shipment, drug return instructions, and any applicable forms. Medication should be examined immediately upon arrival at the study center. The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received and recorded, handled, and stored safely and properly in accordance with GCP, CFR, and local regulations, and used in accordance with this protocol.

The study drugs (droxidopa and carbidopa) must be kept in a secure, limited-access storage area, under the appropriate conditions: store at 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F-86°F). Only authorized personnel will have access to the study drugs at the study centers.

The study drugs will be dispensed to the patient at the study center by a person authorized by the study investigator at each scheduled visit. The patient will return all bottles of the study drug, whether unopened, partially full, or empty at each visit.

A record of study drug accountability (ie, study drug and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused bottles of study drug will be returned to the sponsor or its designee for destruction.

Concomitant Interventions

5.1.1 Required Interventions

The required interventions include taking droxidopa and carbidopa according to the regimen described above.

5.1.2 Prohibited Interventions

Disallowed and Allowed Medications Before Study Drug Treatment

The following previous medications will be disallowed before study drug treatment:

- Any investigational products within 60 days prior to the Screening/Baseline Visit
- Droxidopa or any vasoconstricting agents within 30 days prior to the Screening/Baseline Visit
- Any medications which increase blood pressure, including norepinephrine, ephedrine, midodrine, fludrocortisone, and triptans
- Any other noradrenergic medications, such as serotonin-norepinephrine reuptake inhibitors (SNRI's)

The following previous medications will be allowed:

- Dopaminergic medication – the dose must be stable for greater than or equal to 30 days prior to the Screening Visit
- Amantadine – the dose must be stable for greater than or equal to 30 days prior to the Screening Visit

Disallowed and Allowed Medications During Study Drug Treatment

The following medications will be disallowed during the study:

- Any medications which increase blood pressure, including norepinephrine, ephedrine, midodrine, fludrocortisone, and triptans
- Any other noradrenergic medications, such as serotonin-norepinephrine reuptake inhibitors (SNRI's)

The following medications will be allowed during the study:

- Dopaminergic medication: ropinirole, pramipexole, rotigotine, levodopa, and entacapone
- Amantadine

5.1.3 Precautionary Interventions

During the titration phase, subjects will be monitored closely for any adverse reactions. If any should occur, the subject will be decreased back to the maximum tolerated dose. If any adverse reactions develop that result in discontinuation of the medication or study protocol, this will be documented as an adverse event.

Adherence Assessment

At each study visit, the investigator or site coordinator will assess the patient's compliance with the study requirements. This will include checks of protocol compliance and treatment compliance. During the titration period, patients will be asked about any difficulties following the titration and dosing schedule. At each study visit, the subject will be instructed to bring their pill bottles with them and the number of remaining pills of both droxidopa and carbidopa will be counted and recorded. Treatment compliance will be defined as those taking greater than or equal to 70% of the assigned study drug doses. The modified intent-to-treat (mITT) population will be used for all analyses. The mITT population is all participants who begin the study and who have at least 1 post-baseline assessment. Patients who fail to comply with the study requirements may be withdrawn from the study.

6 CLINICAL AND LABORATORY EVALUATIONS**Schedule of Evaluations**

Procedures and assessments	Screening	Baseline	Study Visit 1	Phone visit during titration	Study Visit 2	Study Visit 3	Study Visit 4
Medical history	X						
Medication history	X						
Inclusion and exclusion criteria	X						
Physical examination	X	X	X		X	X	X
Orthostatic vital signs	X	X	X		X	X	X
UPDRS Parts 2 and 3 ¹⁸	X		X			X	X
MoCA ¹⁹	X						
Hoehn and Yahr staging ²⁰	X						
GDS-15 symptoms score ²¹	X						
Informed consent	X						
Concomitant medication inquiry	X	X	X		X	X	X
Stop Signal task ²²	X	X	X			X	X
Simon task ²³		X	X			X	X
Reward learning task ³⁴		X	X			X	X
FrSBe scale ²⁵		X	X			X	X
Fall diary		X	X			X	X
MRI brain		X	X			X	
Autonomic function testing		X	X			X	
Blood catecholamine measurement		X				X	
Transcranial Doppler US		X				X	
GAITRite assessment ²⁶		X				X	X
Adverse event inquiry		X	X	X	X	X	X
Dispense/collect study drug		X	X		X	X	X

UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; GDS-15, Geriatric Depression Scale; FrSBe scale, Frontal Systems Behavior Scale

Timing of Evaluations

6.1.1.1 Pre-Randomization Evaluations

Procedures for Screening/Baseline

A signed and dated informed consent form will be obtained before screening procedures commence. Once the informed consent form is signed, all screening/baseline procedures need to be completed within 5 days. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations, with clear documentation within the source documents. In addition, disease-specific assessments performed within a specified time frame prior to informed consent may be used for the study. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened will be assigned an identification number.

A patient who is screened and does not meet study entry criteria will not be considered for screening again.

At the initial Screening Visit, a comprehensive review of the medical history and current medications will be performed. UPDRS score will be determined based on clinical examination. Blood pressure and heart rate will be recorded in the supine, sitting, and standing positions and an ECG will be performed. Each subject will also undergo screening cognitive testing including a MOCA (Montreal Cognitive Assessment), RBANS, Trails A and B, and categorical fluency tests. If all inclusion and exclusion criteria are satisfied, written informed consent will be obtained.

The following procedures will be performed at the Screening Visit:

- Inform patients of study restrictions and compliance requirements.
- Obtain written informed consent before any other study-related procedures are performed.
- Medical history review
- Medication history review
- Confirm the patient has a diagnosis of idiopathic PD based on the UK
- Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (refer to
- Appendix C).
- UPDRS, Parts 2 and 3, completed by a trained site rater (PI or designee)
- Hoehn and Yahr staging
- Montreal Cognitive Assessment (MoCA), Version 7.1, rating scale
- GDS-15 symptoms score < 10
- Physical examination (including height and weight)
- Vital signs measurements (pulse and blood pressure recorded after 3 minutes supine and 3 minutes standing)
- Review inclusion and exclusion criteria.

At the subsequent Baseline Visit, all subjects will undergo initial cognitive assessments including the Stop-Signal, Simon, and Attentional blink tasks. An initial gait assessment using the GAITRite system will also be performed. This will include assessments of timed up and go, straight away, walking as fast as possible,

walking as fast as possible through a door, and walking as fast as possible through a door while performing serial 7's. Postural reflexes will also be assessed using a pull test on the gait mat. Orthostatic vital signs will also be checked at this visit.

The following procedures will be performed at the Baseline Visit:

- Stop-Signal Task
- Simon Task
- Attentional Blink Task
- Reward Learning Task
- Initial GAITRite assessment
- Autonomic function testing
- MRI brain

6.1.1.2 On-Study/On-Intervention Evaluations

Procedures During Study Drug Treatment

After the Baseline Visit, each subject will be started on a stable dose of carbidopa to reach a total of 200mg BID. This will be continued for the next week until Study Visit 1. Study visits must be scheduled on the weeks indicated in the Schedule of Evaluations +/- 5 days.

Study Visit 1

The following procedures will be performed at Study Visit 1:

- Stop-Signal Task
- Simon Task
- Attentional Blink Task
- Reward Learning Task
- Autonomic function testing, including orthostatic vital signs
- MRI brain
- Ask the patient, "How have you been feeling?" and record any AEs that are reported.
- Verify all concomitant medications (total daily dose must be recorded for all PD medications) and record any changes.
- Record any interruptions in study drug dosing. Count and record the number of remaining tablets of study drug that were dispensed at the previous visit.
- Count and dispense 1 new bottle of study drug to the patient.

After Study Visit 1, each subject will begin titration of droxidopa over the next week. Study Visit 2 will take place once each subject is stabilized on the maximum tolerated dose. At this visit, repeat cognitive assessments (Stop-Signal, Simon, and Attentional blink tasks) and a gait assessment will be performed. Orthostatic vital signs will also be measured.

Study Visit 2

- Vital signs measurements (pulse and blood pressure recorded after 3 minutes supine and 3 minutes standing)
- Ask the patient, “How have you been feeling?” and record any AEs that are reported.
- Verify all concomitant medications (total daily dose must be recorded for all PD medications) and record any changes.
- Record any interruptions in study drug dosing. Count and record the number of remaining tablets of study drug that were dispensed at the previous visit.
- Count and dispense 1 new bottle of study drug to the patient.

Study Visit 3

- Stop-Signal Task
- Simon Task
- Attentional Blink Task
- Reward Learning Task
- GAITRite analysis
- Autonomic function testing, including orthostatic vital signs, transcranial Doppler, and blood catecholamine measurement
- MRI brain
- Ask the patient, “How have you been feeling?” and record any AEs that are reported.
- Verify all concomitant medications (total daily dose must be recorded for all PD medications) and record any changes.
- Record any interruptions in study drug dosing. Count and record the number of remaining tablets of study drug that were dispensed at the previous visit.
- Provide instructions for tapering droxidopa and carbidopa

6.1.1.3 Intervention Discontinuation Evaluations

All subjects who discontinue the study medications will continue to be followed and will be included in the final analysis in an intention-to-treat model.

6.1.1.4 On Study/Off-Intervention Evaluations

After Study Visit 3 has been completed, each subject will be tapered off droxidopa and carbidopa. The final visit will take place after a one month washout period and will again include cognitive testing and a gait assessment. During the washout period there will be two phone visits to check in with the subject and inquire about any adverse events.

6.1.1.5 Final On-Study Evaluations

Study Visit 4 (Final Visit)

The Final Visit will take place after a one month washout period and will again include cognitive testing and a gait assessment.

Patients who participate in the study in compliance with the protocol for 3 weeks of treatment will be considered to have completed the study.

If a patient withdraws from the study during the treatment period, the reason must be determined and recorded. For patients who withdraw consent, every attempt will be made to determine the reason.

The following procedures and assessments will be performed at the Final Visit:

- Stop-Signal Task
- Simon Task
- Attentional Blink Task
- Reward Learning Task
- GAITRite analysis
- Vital signs measurements (pulse and blood pressure recorded after 3 minutes supine and 3 minutes standing)
- Ask the patient, “How have you been feeling?” and record any AEs that are reported.
- Verify all concomitant medications (total daily dose must be recorded for all PD medications) and record any changes.
- Record any interruptions in study drug dosing. Count and record the number of remaining tablets of study drug that were dispensed at the previous visit. Retrieve all unused study drug for accountability.

6.1.1.6 Off-Study Requirements

No formal study visits are planned after the completion of Study Visit 4. Patients will be provided with our contact information and will be encouraged to call with any questions or concerns and to notify the investigator of any new adverse events.

Special Instructions and Definitions of Evaluations

6.1.2 Informed Consent

The investigator will fully inform the patient of all pertinent aspects of the study, including the written information approved by the IRB/EC. Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IRB/EC requirements. The patient’s willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The investigator will keep the original consent forms, and copies will be

given to the patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the patient will be given to all patients with ample time for their consent.

6.1.3 Documentation of Parkinson's disease

The diagnosis of idiopathic Parkinson's disease will be verified based on the UK Parkinson Disease Society Brain Bank Clinical Diagnostic Criteria. UPDRS rating scales will also be performed to document severity and motor subtype. Hoehn and Yahr staging will also be performed to document disease severity and functional impairment.

6.1.4 Medical History

A comprehensive medical history will be obtained at the Screening Visit.

6.1.5 Treatment History

Documentation of all current and previous medications for 90 days prior to the screening visit.

6.1.6 Concomitant Treatments

All concomitant medications will be documented, and specific inquiry will address any prohibited concomitant therapies.

6.1.7 Clinical Assessments

A general physical exam, neurologic exam, and orthostatic vital signs will be performed at all study visits.

6.1.8 Laboratory Evaluations

Blood catecholamine levels will be checked at Baseline and Study Visit 3.

6.1.9 Pharmacokinetic Studies

N/a

6.1.10 Other Laboratory Studies

N/a

6.1.11 Additional Evaluations

Stop Signal task

The Stop-Signal Task (22) measures the speed with which an initiated action can be inhibited upon the occurrence of a stopping stimulus. In this task, participants are presented with a green arrow on a screen pointing either to the left or the right and are instructed to press a button with the left or right index finger, corresponding to the direction of the arrow. For the majority of the trials the arrow remains green and subjects respond as instructed. However on a certain percentage (typically 30%) of the trials, the arrow turns red shortly after appearing on the screen. This signals the participant to inhibit the previously initiated response and refrain from pressing the button. The delay between the presentation of the arrow and the presentation of the stop signal can be varied to adjust the difficulty of the task, as it is easier to suppress a response the earlier the signal appears. This delay is automatically adjusted during the task in order for each subject to achieve successful inhibition on 50% of the “stop” trials.

The Stop-Signal Reaction Time (SSRT) is calculated as the difference between the average response time on “go” trials and the average stop signal delay. The SSRT reflects the time it takes an individual to stop a previously initiated action. It has been extensively studied as a measure of inhibitory action control. Slower SSRT's have been associated with a number of disease processes but seem to be most closely linked to disorders affecting the prefrontal cortex (27,28) and basal ganglia (29,30,31).

The Stop-Signal Task will be completed at the Baseline Visit as well as Study Visits 1, 2, 3, and 4.

Simon task

The Simon task (23) is another well-validated measure of inhibitory action control which has also been studied extensively in PD. This is a conflict task which measures the effect of interfering impulses on the ability to select a goal response. Participants are instructed to respond with either the left or right hand according to the color of a stimulus. However, the stimuli are presented either to the left or to the right of a fixation point. The spatial location of the stimulus, although irrelevant to the goal of the task, elicits an impulse to respond with the corresponding hand. Therefore, on trials in which the location of the stimulus matches the response signaled by the color, both reaction time and accuracy are facilitated (corresponding trials). On non-corresponding trials the impulsive response activated by location and the slower controlled response based on color are incompatible, therefore slowing reaction time and increasing error rates. The Simon Effect refers to the magnitude of this interference, or the difference in reaction time between compatible and incompatible trials.

Accuracy rates on the Simon task tend to be lower in trials with short reaction times, due to an increase in the proportion of fast impulsive errors. Plotting the accuracy rates for incompatible trials as a function of reaction time thus generates a conditional accuracy function (CAF). Accuracy rates for the fastest group of reaction times are used as an indicator of impulsivity and have been shown to be the most sensitive measure of automatic response capture (32).

Previous studies indicate that PD reduces the proficiency of suppressing impulsive actions (32), and inhibitory control worsens with increasing disease severity. Furthermore, PD patients who fall into the PIGD subtype make significantly more impulsive errors than tremor dominant patients. This indicates that patients with gait dysfunction are more likely to react impulsively, which may correlate with fall risk. In addition,

these results also lend further support to the critical link between impaired action control and gait dysfunction in PD.

Attentional blink task

The attentional blink task (24) is a measure of visual attention, a process that has been found to be very closely linked to norepinephrine. Subjects are presented with a series of letters in rapid serial visual presentation (RSVP). They are asked to identify a specified letter, and then to report a second target letter which appears after a variable delay from the first target letter. The ability to report the second target is diminished when it falls between 200-500ms from the first. The duration of this time period is known as the attentional blink. The size of the attentional blink can vary based on many factors but is thought to be predominantly a norepinephrine-dependent process (33).

Reward learning task

The reward learning task is a probabilistic action–valence learning paradigm during which subjects must learn to act or withhold action in order to maximize monetary earnings by gaining rewards and avoiding losses (34, 35). Specifically, subjects view a series of cartoon characters that are presented one at a time in the center of a computer screen. With each decision to act or withhold action, subjects receive monetary feedback (reward, punishment, or no monetary outcome). Unbeknownst to the subject, two of the cartoon characters provide outcomes that will be either rewarded or unrewarded, and the remaining two characters provide outcomes that will be either punished or unpunished. Therefore, the former characters will be associated with reward learning, whereas the latter characters will be associated with punishment avoidance learning. Also unknown to the subject, one character from each set yields the optimal outcome (i.e., either gain reward or avoid punishment) by acting, but the other character from each set yields the optimal outcome by withholding action.

We will calculate accuracy for each of the four action-valence combinations (action-reward, action-punishment, inaction-reward, inaction-punishment), defined by the percentage of trials in which the subject selected the optimal response in the final 10 trials (from a total of 40 learning trials).

MRI brain

MRI scans of the brain will be performed at baseline, on carbidopa, and on carbidopa+droxidopa using thin section inversion prepared T1-weighted gradient echo sequences (IR SPGR, TE=3.6, TR=19, TI=400, 24 cm field of view) in the sagittal (slice thickness 1.2 mm) and coronal (slice thickness 1.4 mm) planes. In addition, fast spin echo axial spin density weighted (TE=19, TR=5000, 3 mm thick) and T2-weighted (TE=106, TR=5000, 3 mm thick) slices will be obtained to exclude any structural abnormalities. After structural imaging, resting state BOLD signal imaging will occur. Whole-brain oxygen extraction fraction can be assessed quickly and noninvasively using MRI. Specifically, the blood water transverse relaxation time (T2) depends very sensitively on oxygenation level¹⁰ and hematocrit (Hct), and therefore combined measurements of Hct and venous T2 can be converted to blood oxygenation level through appropriate blood signal isolation and calibration procedures. Elegant work has demonstrated the dependence between venous T2 and blood oxygenation level, and this so-called TRUST MRI method has recently been devel-

oped and validated for the measurement of OEF.¹¹ TRUST MRI has been used to quantify OEF in healthy adults across the lifespan (36).

Autonomic function testing

Postural study. Participants will be studied in the morning, under fasting condition after midnight to avoid the confounding effect of post-prandial hypotension. We will obtain SBP, DBP and HR measurements with automated sphygmomanometer twice while supine for 10 minutes (with the torso and head elevated 30 degrees from horizontal) and after 1, 3, 5, 15 and 30 minutes while upright. The standing time will be measured by a chronometer. This initial measurement will allow us to determine if patients have OH (inclusion criterion).

Autonomic function testing. All patients enrolled in this study will undergo autonomic function tests to determine the presence of autonomic failure. During these tests, we will monitor HR by EKG and blood pressure continuously with tonometry or finger plethysmography and intermittently with an oscillometric device. These tests include sinus arrhythmia and valsalva maneuver. Deep breathing-vagally-mediated sinus arrhythmia (SA) will be assessed during controlled breathing (pattern of 5 seconds inhalation and 5 seconds exhalation repeated over 90 seconds). Valsalva maneuver will be assessed by instructing the subject to exhale against a 40 mm Hg pressure. Changes in intra thoracic pressure produce autonomically modulated transient changes in heart rate and blood pressure.

Blood catecholamine measurements. Supine and standing plasma norepinephrine levels will be measured at baseline and at peak dose droxidopa therapy.

Cerebral blood flow. We will use an ST3 digital transcranial doppler system (Spencer technologies, Seattle, WA) to continuously monitor cerebral blood flow velocity during progressive head up tilt. The left MCA will be insonated from the anterior temporal window by placing the probe on the temporal area, above the zygomatic arch. We will fix the probe with the Marc 600 Headframe System (Spencer Technologies, Seattle, WA) for stable positioning. Doppler shift, a difference between the frequency of the emitted signal (2 MHz) and its echo (frequency of the reflected signal), was then used to calculate the velocity of blood flow by means of Fourier transform. An assumption that the diameter of the MCA does not change must be made to relate MCA flow velocity to blood flow. The caliber of the MCA stem (the insonated segment in TCD) is reported to change by <4% in response to BP and CO₂ changes.

GAITRite assessment

The GAITRite gait analysis system is a portable walkway embedded with grids of pressure sensors which record footfalls and provide information regarding a variety of spatial and temporal parameters of gait. It has been validated in a number of populations (37, 38, 39), including Parkinson disease patients (40). Parameters such as gait velocity, cadence (steps per minute), stride length, and ratios of swing and stance phases can be calculated based on the recorded data. Patients can also be asked to perform different tasks on the gait mat, such as a timed up and go test (standing up from a seated position and walking a set distance) or assessments of postural instability such as the pull test. Cognitive tasks can also be added to increase the level of difficulty and sometimes induce freezing in susceptible patients. These include performing serial 7 calculations while walking, walking as fast as possible, and navigating an obstacle such as a door.

Adverse event inquiry

Subjects will be asked open-ended questions about how they have been feeling at each study visit. Adverse event inquiries will be performed at Baseline, Study Visit 1, a Phone Visit during titration, and Study Visits 2, 3, and 4. Any adverse events will be documented and managed as described in Sections 7 and 10.

6.1.12 Questionnaires

- Hoehn and Yahr staging will be performed at Screening.
- Montreal Cognitive Assessment (MoCA), Version 7.1 will be performed at Screening.
- GDS-15 (Geriatric Depression Scale) will be performed at Screening.
- FrSBe scale will be performed at Baseline and Study Visits 1, 3, and 4.
- All subjects will be asked to keep a fall diary throughout the study. This will be reviewed at Baseline and Study Visits 1, 3, and 4.

6.1.13 Adherence Assessments

At each study visit, the investigator or site coordinator will assess the patient's compliance with the study requirements. This will include checks of protocol compliance and treatment compliance. During the titration period, patients will be asked about any difficulties following the titration and dosing schedule. At each study visit, the subject will be instructed to bring their pill bottles with them and the number of remaining pills of both droxidopa and carbidopa will be counted and recorded. Treatment compliance will be defined as those taking greater than or equal to 70% of the assigned study drug doses. The modified intent-to-treat (mITT) population will be used for all analyses. The mITT population is all participants who begin the study and who have at least 1 post-baseline assessment. Patients who fail to comply with the study requirements may be withdrawn from the study.

7 MANAGEMENT OF ADVERSE EXPERIENCES

The safety of combined droxidopa and carbidopa treatment will be assessed by evaluating adverse events (AEs) and vital signs.

The following adverse events have been reported with droxidopa:

- Hypertension (SBP > 180)
- Headache
- Nausea
- Fatigue
- Dizziness

Carbidopa alone has not been associated with any adverse effects. When administered in combination with levodopa, the most common adverse reactions include dyskinesias and nausea. Other reported adverse

reactions include delusions, hallucinations, impulse control behaviors, and depression. Convulsions have also occurred although a causal relationship has not been established.

Administering droxidopa along with carbidopa would be expected to be associated with a reduced risk of hypertension as compared with droxidopa alone, as this is a peripheral effect resulting from arterial and venous vasoconstriction induced directly by norepinephrine. Therefore, inhibiting the peripheral metabolism of droxidopa will limit these effects and increase the central activity of norepinephrine. In the studies performed thus far, no additional adverse events have been reported in those patients treated with droxidopa along with carbidopa as compared with droxidopa alone, although further investigation is warranted.

Vital signs will be measured at the Screening and Baseline Visits as well as Weeks 3, 5, 7, and 11 (or early discontinuation) Visits. Vital signs include pulse and blood pressure. The same position and arm should be used each time vital signs are measured for a given patient. Blood pressure and pulse will be recorded after the patient has been supine for at least 3 minutes, and after standing for 3 minutes. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any increase in systolic blood pressure over 180mmHg will be listed as an adverse event. In addition, any vital sign value that is judged by the investigator as a clinically significant change (worsening) compared to a screening/baseline value will be considered an AE, recorded, and monitored.

Physical examinations, including height and weight will be performed at the Screening/Baseline Visit. Any physical examination finding that is judged by the investigator as a clinically significant finding should be recorded in the medical history or AE sections.

Concomitant therapy or medication usage will be monitored throughout the study. If a subject begins a contraindicated medication during the study period, this must be stopped immediately or the subject must withdraw from the study.

During the titration phase, subjects will be monitored closely for any adverse effects. If any should occur, the subject will be decreased back to the maximum tolerated dose. If the symptoms resolve and the subject is then able to complete the study protocol at the reduced dosage, this will be documented in the dose finding portion of the study. If any adverse reactions develop that result in discontinuation of the medication or study protocol, this will be documented as an adverse event.

The study chair will also work closely with Lundbeck throughout the study period to ensure that toxicities that have been seen in previous studies are identified, and that a plan for management and documentation of these toxicities is developed.

8 CRITERIA FOR INTERVENTION DISCONTINUATION

Criteria for discontinuing the study intervention are as follows:

- Sustained hypertension >180mmHg systolic despite a reduction in droxidopa dose
- Adverse events that do not resolve with dose modification
- Any serious adverse events

All subjects who begin the study and have at least one post-baseline assessment will be included in the final analysis according to the modified intent-to-treat approach. Subjects who discontinue the study intervention will still be encouraged to complete the remainder of the study visits and will be compensated for their time.

9 STATISTICAL CONSIDERATIONS

General Design Issues

This is an 11-week, prospective, open label, safety and tolerability study evaluating combined carbidopa and droxidopa therapy in PD. Our primary hypothesis is that this combination therapy will be safe and tolerable in a cohort of Parkinson disease patients classified as PIGD subtype. The primary outcome measure is therefore the safety (defined as the percent of subjects who develop an adverse event during the study period) and tolerability (defined as the number of patients who discontinue the study medications due to an adverse event) of this combination therapy. Our secondary objectives are to determine the optimal dosing regimen for combined droxidopa and carbidopa therapy in this patient population, and to explore the effects of central norepinephrine repletion on action control in Parkinson's disease patients. These objectives will provide preliminary data to be used in the development of future efficacy trials if the intervention is found to be safe and tolerable in this population.

Outcomes

9.1.1 Primary outcome

Our primary outcome measure will be the safety and tolerability of droxidopa combined with carbidopa in a Parkinson disease cohort.

- Safety will be defined by the percent of subjects who develop an adverse event during the 7-week treatment period that is determined to be likely related to the study medications
 - Predefined safety outcomes:
 - Hypertension (SBP > 180)
 - Headache
 - Nausea
 - Fatigue
 - Dizziness
 - Agitation or adverse behavioral symptoms
- Tolerability will be defined by the number of patients who discontinue the study drug due to adverse effects.

9.1.2 Secondary outcomes

- The mean maximum tolerated dose of droxidopa reached by the study participants and the percent compliance (those who take greater than or equal to 70% of the assigned dosage)
- Change in Stop-Signal reaction time from baseline to Week 7

9.1.3 Exploratory outcomes

- Change in performance on exploratory measures from baseline to Week 7: Simon task, attentional blink, gait assessment, and imaging and autonomic data

Sample Size and Accrual

Our primary hypothesis is that combination droxidopa and carbidopa therapy will be safe and tolerable in this cohort of PD patients.

The primary safety outcome is the percent of subjects who are able to complete the study protocol without any AE's leading to discontinuation. In the initial safety and tolerability studies leading to the approval of droxidopa, adverse effects leading to discontinuation occurred in approximately 18% of patients. The most common AE's leading to discontinuation were nausea or hypertension. We will therefore set our accepted toxicity rate at 20%. Given an alpha of 0.05 and a B of 0.10 to provide 90% power, a sample size of 15 patients will be sufficient to determine our primary safety outcome.

Our secondary outcomes include some preliminary efficacy measures to inform the development of future trials. We will use a change in Stop-Signal Reaction Time as our secondary efficacy variable. Based on a within-subject analysis comparing three measurements (screening, baseline, and on medication), we calculated that a sample size of 14 subjects would be sufficient to obtain significant medication effects on inhibition in the Stop Signal task. This is based on a repeated measures ANOVA with an effect size of 0.57 (based on previous studies), alpha 0.05, and power of 0.9.

Data Monitoring

All patients will be monitored for adverse events related to medication as described above. Patient data and results will be monitored at intervals throughout the study.

An independent data safety monitor has been identified for this study. Monthly meetings will be conducted to review data and safety issues. We will review any adverse events immediately with the safety monitor.

Data Analyses

The modified intent-to-treat (mITT) population will be used for all analyses. The mITT population is all participants who begin the study and have at least 1 post-baseline assessment.

The overall safety and tolerability of combined droxidopa and carbidopa treatment will be assessed throughout the study by evaluating AE's and vital signs and the number (%) of patients who discontinue the study and the number (%) of patients who discontinue the study due to an AE.

A preliminary efficacy analysis will be performed using a repeated measures ANOVA to compare Stop-Signal Reaction time at the Baseline Visit, Study Visit 1, and Study Visit 3

9.8.2. Safety Analysis

All AEs will be coded using the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA). A patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all AEs (overall and by severity), AEs determined by the investigator to be treatment related (defined as possibly related or with missing relationship) (overall and by severity), SAEs, and AEs causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of deaths, serious AEs, and AEs leading to withdrawal will be presented.

Descriptive statistics of vital signs, as well as their changes from baseline, will be presented by treatment group. Changes in vital signs measurement data will be summarized descriptively. All values will be compared to prespecified boundaries so that potentially clinically significant changes or values can be identified, and such values will be listed. The frequency of potentially clinically significant vital sign measurements will be presented by treatment group.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

Descriptive summaries of SAEs, patient withdrawals due to AEs, and potentially clinically significant abnormal values (clinical laboratory or vital signs) on the basis of predefined criteria will also be provided.

9.8.3. Tolerability Analysis

Tolerability analysis will be based on the number and percent of patients who discontinue the study drug and the number and percent of patients who terminate the study drug due to AEs. Time to withdrawal of study drug will be presented by Kaplan-Meier curves. Significance testing of time to withdrawal of study drug will be done using a log-rank test.

10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

Records to Be Kept

The medical experts, study monitors, auditors, IRB/EC, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts or records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

Each investigator must maintain, at all times, the original records (ie, source documents) of each patient's data. Examples of source documents are hospital records, office visit records, examining physician's findings or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol-required worksheets, and case report forms (CRFs) that are used as the source.

Each investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

10.1.1 Role of Data Management

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS). Before it is used to capture data from this study, the CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study. Before using the CDMS, all users will receive training on the system and any study-specific training. Subsequent to the training, the users will be provided with individual system access right.

Data will be collected at the study center by appropriately designated and trained personnel, and CRFs must be completed for each patient screened who provided informed consent according to the data source. The patient's identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by data management using both automated logical checks and manual review. All data collected will be approved by the investigator at the study center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate. If data are processed from other institutions (ie, central laboratory, central image center, electronic diary data), the results should be sent to the study center and be sent electronically to the sponsor (or organization performing data management) for direct application into the clinical database (see Section 3.9). Laboratory test results will not be added to the CRF unless otherwise noted in the protocol. For subjects who are designated as screening failures, only data for demography, disposition, and AEs will be entered into the clinical database.

Data management is responsible for the accuracy, quality, completeness, and internal consistency of the data from the study. Data handling, including data quality assurance, will comply with worldwide regulatory guidelines (eg, ICH, GCP). Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data management plan. When data management is outsourced, the contract research organization (CRO) will be responsible for the development and implementation of the data management plan.

Received CRFs will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried. When data management is outsourced, the CRO will be responsible for the database quality assurance, including, but not limited to, all applicable coded terms.

Data corrections in the CDMS will be made using the CDMS update function. For each instance of data modifications, the system requires a reason for the change. The system keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. During or at the end of the study, the Lundbeck Clinical Quality Assurance Group will be responsible for the audit of the study process and documentation.

Quality Assurance

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IRB/EC, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration. Each principal investigator and the sponsor will sign the protocol amendment.

Study Monitoring

To ensure compliance with GCP guidelines, a study safety monitor will be appointed. Regular meetings will be conducted to review data and safety issues. All unanticipated adverse events will be reported to the IRB within 7 days of their occurrence, and within 10 days to the FDA.

Audit and Inspection

The sponsor may audit the study center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The sponsor quality assurance unit, independent of the clinical research department, is responsible for determining the need for and timing of a study center audit. Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance of the study with GCP guidelines.

Adverse Experience Reporting

An adverse event is any untoward medical occurrence in a patient that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product or a device and does not necessarily have a causal relationship to the study drug.

In the study, any event occurring after the clinical study patient has signed informed consent should be recorded and reported as an AE, except for screening/baseline laboratory, ECG, and physical examination findings that are done for screening/baseline prior to the start of study drug administration.

For the purpose of AE recording, the study period is defined as that time period from signature of the informed consent form through the end of the follow-up period. For this study, the follow-up period is defined as 30 days following the last dose of study drug.

All AEs that occur during the defined study period must be recorded, regardless of the severity of the event or judged relationship to the study drug. All FDA, OHRP and local IRB requirements for reporting adverse experiences must be followed.

At each contact with the patient, the investigator or designee must query the patient for AEs by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively.

The clinical course of each AE will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; the patient is referred to the care of a local health care professional; or a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of AE duration less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each AE must be recorded. The relationship of each AE to study drug treatment and study procedures, and the severity and seriousness of each AE, as judged by the investigator, must be recorded as described in the Manual of Operations.

Summaries will be presented for all AEs (overall and by severity), AEs determined by the investigator to be treatment related, serious adverse events (SAEs), and AEs causing withdrawal from the study. Patient listings of deaths, SAEs, and AEs leading to withdrawal will be presented.

Severity of an Adverse Event

The severity of each AE must be recorded as one of the following choices:

- Mild: No limitation of usual activities
- Moderate: Some limitation of usual activities
- Severe: Inability to carry out usual activities

Relationship of an Adverse Event to the Study Drug

The relationship of an AE to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility/Not related	This category applies to those AEs that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to those AEs that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	An adverse experience may be considered having no reasonable possibility if it is clearly due to extraneous causes or when it meets at least 2 of the following criteria: <ul style="list-style-type: none"> It does not follow a reasonable temporal sequence from the administration of the test drug. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. It does not follow a known pattern of response to the test drug. It does not reappear or worsen when the drug is readministered.
Reasonable possibility/Related	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the study drug.	An adverse experience may be considered having reasonable possibility related if or when it meets at least 2 of the following criteria: <ul style="list-style-type: none"> It follows a reasonable temporal sequence from administration of the drug. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. It follows a known pattern of response to the test drug.

Serious Adverse Events

A serious adverse event (SAE) is an AE occurring at any dose that results in any of the following outcomes or actions:

- Death
- A life-threatening AE (ie, in the view of either the investigator or the sponsor, the patient was at immediate risk of death from the event as it occurred) does not include an event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission or prolongation of hospital stay was required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a preexisting condition that has not worsened during participation in the study will not be considered SAEs.
- Substantial disruption of the patient's ability to conduct normal life functions, ie, the adverse event resulted in a significant, persistent or permanent change, impairment, damage, or disruption in the patient's body function or structure, physical activities, or quality of life

- A congenital anomaly or birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. NOTE: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An AE that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious AE.

Expectedness

An unlabeled or unexpected SAE is a reaction that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency. The labeling reference for this study is the Northera prescribing information (refer to Appendix A).

Sponsor pharmacovigilance will help to determine the expectedness for all SAEs.

All SAEs that occur during the study period (including the protocol-defined follow-up period), regardless of judged relationship to treatment with the study drug, must be immediately reported to the sponsor or designee by the investigator. All SAEs that occur after the study period, if considered related to study drug treatment or to the patient's participation in the study, must also be immediately reported to the sponsor or designee by the investigator.

The report must be made within 24 hours of the investigator's knowledge of the event or, if the event occurs on a weekend or national holiday, at the latest, on the following working day.

To satisfy regulatory requirements, any SAE, whether deemed IMP-related or not, must be reported to the sponsor or designee as soon as possible after the investigator or coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact.

The SAE report should be submitted to the sponsor or designee within 24 hours of becoming aware of the event. The sponsor or designee will forward the report to the pharmacovigilance unit.

The following information should be provided to accurately and completely record the event:

- study number
- investigator and center identification
- patient number
- patient initials
- AE term
- serious criteria
- investigator's assessment of the relationship of the AE to the study drug

Additional information may include the following:

- age and sex of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- onset date and description of AE
- action taken
- outcome, if known
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge or rechallenge, if know
- If the AE results in death:
 - cause of death (whether or not the death was related to study drug)
 - autopsy findings (if available)

Withdrawal Due to an Adverse Event

Any patient who experiences an AE may be withdrawn from the study drug at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an AE, both the AEs page and discontinuation page of the CRF will be completed at that time. The patient will be monitored until the event has resolved or stabilized, until a determination of a cause unrelated to the study drug or study procedure is made, or until the patient is referred to the care of a local health care professional. The investigator must inform the medical monitor as soon as possible of all patients who are being considered for withdrawal due to AEs. Additional reports must be provided when requested.

If a patient is withdrawn from the study drug for multiple reasons that include AEs, the discontinuation page of the CRF should indicate that the withdrawal was related to an AE. An exception to this requirement will be the occurrence of an AE that, in the opinion of the investigator, is not severe enough to warrant discontinuation, but which requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be the need to take a prohibited medication, not the AE.

Protocol Deviations Because of an Adverse Event

If a patient experiences an AE or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization or treatment for the emergency to protect patient safety has been administered, the investigator or other physician in attendance in such an emergency must contact the individual identified in the clinical study personnel contact information section of this protocol, as soon as possible, to discuss the circumstances of the emergency. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

Institutional Review Board (IRB) Review and Informed Consent

The investigator will fully inform the patient of all pertinent aspects of the study, including the written information approved by the IRB/EC. Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IRB/EC requirements. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The investigator will keep the original consent forms, and copies will be given to the patient. It will also be explained to the patient that he or she is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the patient will be given to all patients with ample time for their consent.

Subject Confidentiality

Each investigator must assure that the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number). All records will be kept in a locked file cabinet. All electronic data will be entered using the identification code only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data recorded on the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

The sponsor is responsible for preparing a clinical study report, in cooperation with the principal investigator. The final report is signed by the sponsor and, if applicable, by the principal investigator.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the principal investigator for comments and suggestions. An endorsement of the final report will be sought from the principal investigator when required by local regulatory agencies.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the current “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, collection of data or analysis, interpretation of data, and manuscript preparation. The publications committee established by the sponsor will oversee this process. Additional publications may follow the first. Policies regarding the publication of the study results are defined in the financial agreement.

No patent application based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

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APPENDIX A

Nothera Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NORTHERA safely and effectively. See full prescribing information for NORTHERA.

NORTHERA™ (droxidopa) capsules, for oral use

Initial U.S. Approval: 2014

DOSAGE FORMS AND STRENGTHS

- 100 mg, 200 mg, and 300 mg capsules (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

WARNING: SUPINE HYPERTENSION

See full prescribing information for complete boxed warning.

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA [see *Warnings and Precautions* (5.1)].

INDICATIONS AND USAGE

NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of NORTHERA should be assessed periodically (1).

DOSAGE AND ADMINISTRATION

- Starting dose is 100 mg three times during the day (2.1)
- Titrate by 100 mg three times daily, up to a maximum dose of 600 mg three times daily (2.1)
- Take consistently with or without food (2.1)
- To reduce the potential for supine hypertension, elevate the head of the bed and give the last dose at least 3 hours prior to bedtime (2.1)
- Take NORTHERA capsule whole (2.1)

- NORTHERA can cause supine hypertension and may increase cardiovascular risk if supine hypertension is not well-managed (5.1).
- Hyperpyrexia and confusion (5.2)
- May exacerbate symptoms in patients with existing ischemic heart disease, arrhythmias, and congestive heart failure (5.3)
- Allergic reactions (5.4)

ADVERSE REACTIONS

Headache, dizziness, nausea, hypertension, and fatigue (greater than 5%) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck at 1-800-455-1141 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Use of DOPA decarboxylase inhibitors may require dose adjustments for NORTHERA (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers:* Choose nursing or NORTHERA (8.3)
- Patients with Renal Impairment:* Dosing recommendations cannot be provided for patients with GFR less than 30 mL/min (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2014

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WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure [Parkinson's disease (PD), multiple system atrophy, and pure autonomic failure], dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been established. The continued effectiveness of NORTHERA should be assessed periodically.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of NORTHERA is 100 mg, taken orally three times daily: upon arising in the morning, at midday, and in the late afternoon at least 3 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Administer NORTHERA consistently, either with food or without food. Take NORTHERA capsule whole. Titrate to symptomatic response, in increments of 100 mg three times daily every 24 to 48 hours up to a maximum dose of 600 mg three times daily (i.e., a maximum total daily dose of 1,800 mg).

Monitor supine blood pressure prior to initiating NORTHERA and after increasing the dose.

Patients who miss a dose of NORTHERA should take their next scheduled dose.

3 DOSAGE FORMS AND STRENGTHS

NORTHERA capsules are available in 100 mg, 200 mg, and 300 mg strengths as specified below.

- 100 mg: Hard gelatin capsules with “Nothera” on the white body and “100” on the light blue cap

- 200 mg: Hard gelatin capsules with “Northera” on the white body and “200” on the light yellow cap
- 300 mg: Hard gelatin capsules with “Northera” on the white body and “300” on the light green cap

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Supine Hypertension

NORTHERA therapy may cause or exacerbate supine hypertension in patients with NOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Monitor blood pressure, both in the supine position and in the recommended head-elevated sleeping position. Reduce or discontinue NORTHERA if supine hypertension persists. If supine hypertension is not well-managed, NORTHERA may increase the risk of cardiovascular events.

5.2 Hyperpyrexia and Confusion

Post-marketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with NORTHERA use during post-marketing surveillance in Japan. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients.

5.3 Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure

NORTHERA may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Careful consideration should be given to this potential risk prior to initiating therapy in patients with these conditions.

5.4 Allergic Reactions

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS

The following adverse reactions with NORTHERA are included in more detail in the Warnings and Precautions section of the label:

- Supine Hypertension [see Warnings and Precautions (5.1)]
- Hyperpyrexia and Confusion [see Warnings and Precautions (5.2)]
- May exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety evaluation of NORTHERA is based on two placebo-controlled studies 1 to 2 weeks in duration (Studies 301 and 302), one 8-week placebo-controlled study (Study 306), and two long-term, open-label extension studies (Studies 303 and 304). In the placebo-controlled studies, a total of 485 patients with Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy were randomized and treated, 245 with NORTHERA and 240 with placebo [see Clinical Studies (14)].

Placebo-Controlled Experience

The most commonly observed adverse reactions (those occurring at an incidence of greater than 5% in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group) in NORTHERA-treated patients during the three placebo-controlled trials were headache, dizziness, nausea, hypertension. The most common adverse reactions leading to discontinuation from NORTHERA were hypertension or increased blood pressure and nausea.

Table 1. Most Common Adverse Reactions Occurring More Frequently in the NORTHERA Group

	Study 301 and Study 302 (1 to 2 Weeks Randomized Treatment)		Study 306 (8 to 10 Weeks Randomized Treatment)	
	Placebo (N=132) n (%)	NORTHERA (N=131) n (%)	Placebo (N=108) n (%)	NORTHERA (N=114) n (%)
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)

Note: n=number of patients. Table displays adverse reactions that were reported in greater than 5% of patients in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group.

Long-Term, Open-Label Trials with NORTHERA

In the long-term, open-label extension studies, a total of 422 patients, mean age 65 years, were treated with NORTHERA for a mean total exposure of approximately one year. The commonly reported adverse events were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).

7 DRUG INTERACTIONS

7.1 Drugs that Increase Blood Pressure

Administering NORTHERA in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension.

7.2 Parkinson's Medications

Dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled trials in pregnant women.

Following consecutive oral administration at doses of 60, 200, and 600 mg/kg/day to pregnant Sprague Dawley rats, increased incidences of lower body weight and occurrence of undulant rib were noted in fetuses, but they were slight and spontaneously reversed after birth. Based on dose per unit body surface area, these three doses correspond to approximately 0.3, 1, and 3 times, respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient. Shortening of the gestation period was observed in rats at 600 mg/kg/day. Low incidences of renal lesions (cysts, indentations, or renal pelvic dilation) were observed on the surface of the kidneys of female rats treated with droxidopa during the period of fetal organogenesis. No other potentially teratogenic effects have been observed in rats or rabbits.

8.3 Nursing Mothers

Choose nursing or NORTHERA. In rats, droxidopa is excreted in breast milk, and when the drug was administered to the nursing dams during the period of lactation, reduced weight gain and reduced survival were observed in the offspring.

8.4 Pediatric Use

The safety and effectiveness of NORTHERA in pediatric patients have not been established.

8.5 Geriatric Use

A total of 197 patients with symptomatic NOH aged 75 years or above were included in the NORTHERA clinical program. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Renal Impairment

NORTHERA and its metabolites are primarily cleared renally. Patients with mild or moderate renal impairment (GFR greater than 30 mL/min) were included in clinical trials and did not have a higher frequency of adverse reactions. Clinical experience with NORTHERA in patients with severe renal function impairment (GFR less than 30 mL/min) is limited.

10 OVERDOSAGE

10.1 Symptoms

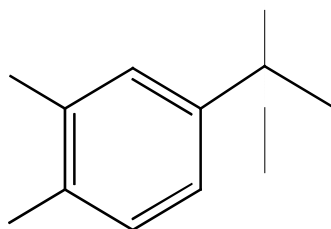
There was one case of overdose reported during post-marketing surveillance in Japan. The patient ingested 7,700 mg of NORTHERA and experienced a hypertensive crisis that resolved promptly with treatment.

10.2 Treatment

There is no known antidote for NORTHERA overdose. In case of an overdose that may result in an excessively high blood pressure, discontinue NORTHERA and treat with appropriate symptomatic and supportive therapy. Counsel patients to remain in a standing or seated position until their blood pressure drops below an acceptable limit.

11 DESCRIPTION

NORTHERA capsules contain droxidopa, which is a synthetic amino acid precursor of norepinephrine, for oral administration. Chemically, droxidopa is (–)-threo-3-(3,4-Dihydroxyphenyl)-L-serine. It has the following structural formula:



Droxidopa is an odorless, tasteless, white to off-white crystals or crystalline powder. It is slightly soluble in water, and practically insoluble in methanol, glacial acetic acid, ethanol, acetone, ether, and chloroform. It is soluble in dilute hydrochloric acid. It has a molecular weight of 213.19 and a molecular formula of $C_9H_{11}NO_5$.

NORTHERA capsules also contain the following inactive ingredients: mannitol, corn starch, and magnesium stearate. The capsule shell is printed with black ink. The black inks contain shellac glaze, ethanol, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol, and ammonium hydroxide. The capsule shell contains the following inactive ingredients: 100 mg – gelatin, titanium dioxide, FD&C Blue No. 2, black and red iron oxide; 200 mg – gelatin, titanium dioxide, FD&C Blue No. 2, black and yellow iron oxide; 300 mg – gelatin, titanium dioxide, FD&C Blue No. 1, FD&C Yellow No. 5 (tartrazine), and FD&C Red No. 40. NORTHERA capsules differ in size and color by strength [see *Dosage Forms and Strengths* (3)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of NORTHERA in the treatment of neurogenic orthostatic hypotension is unknown. NORTHERA is a synthetic amino acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, which is extensively distributed throughout the body. NORTHERA is believed to exert its pharmacological effects through norepinephrine and not through the parent molecule or other metabolites. Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction. NORTHERA in humans induces small and transient rises in plasma norepinephrine.

12.2 Pharmacodynamics

Peak droxidopa plasma concentrations are associated with increases in systolic and diastolic blood pressures. Droxidopa has no clinically significant effect on standing or supine heart rates in patients with autonomic failure.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with NORTHERA at single oral doses up to 2,000 mg, as shown in a dedicated thorough QT study.

12.3 Pharmacokinetics

Absorption

Peak plasma concentrations (C_{\max}) of droxidopa were reached by 1 to 4 hours post-dose (mean of approximately 2 hours) in healthy volunteers. High-fat meals have a moderate impact on droxidopa exposure with C_{\max} and area under the plasma concentration-time curve (AUC) decreasing by 35% and 20%, respectively. The C_{\max} was delayed by approximately 2 hours with a high-fat meal.

Distribution

Pre-clinical studies suggest that droxidopa can cross the blood brain barrier. Droxidopa exhibits plasma protein binding of 75% at 100 ng/mL and 26% at 10,000 ng/mL. The estimated apparent volume of distribution of droxidopa is about 200 L in humans.

Metabolism

The metabolism of droxidopa is mediated by catecholamine pathway and not through the cytochrome P450 system. Droxidopa is initially converted to methoxylated dihydroxyphenylserine (3-OM-DOPS), a major metabolite, by catechol-O-methyltransferase (COMT), to norepinephrine by DOPA decarboxylase (DDC), or to protocatechualdehyde by DOPS aldolase. After oral dosing in humans, plasma norepinephrine levels peak within 3 to 4 hours but are generally very low (less than 1 ng/mL) and variable with no consistent relationship with dose. The contribution of the metabolites of droxidopa other than norepinephrine to its pharmacological effects is not well understood.

Excretion

The mean elimination half-life of droxidopa is approximately 2.5 hours in humans. The major route of elimination of droxidopa and its metabolites is via the kidneys in both animals and in humans. Studies in animals showed that ~75% of the radio-labeled dose was excreted in urine within 24 hours of oral dosing.

Special Populations

There are no clinically relevant effects of age, body mass index, or sex on the pharmacokinetics of droxidopa. A population pharmacokinetic analysis suggests that hepatic function, assessed by aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin, did not influence the exposure to droxidopa. The controlled clinical trials included patients with mild to moderate renal impairment. No dose adjustments are required in patients with mild to moderate renal impairment.

Drug Interactions

No dedicated drug-drug interaction studies were performed for droxidopa. Patients in the Phase 3 trials with NORTHERA received concomitant levodopa/carbidopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors and other medications used to treat Parkinson's disease. Carbidopa, a peripheral dopa-decarboxylase inhibitor,

could prevent the conversion of NORTHERA to norepinephrine outside of the central nervous system (CNS). Patients taking NORTHERA with L-DOPA/dopa- decarboxylase inhibitor combination drugs had decreased clearance of NORTHERA, an increase in exposure (AUC) to droxidopa of approximately 100%, and an increase in exposure to 3-OM-DOPS of approximately 50%. However, in clinical trials, it was found that the decreased clearance was not associated with a significant need for a different treatment dose or increases in associated adverse events. Dopamine agonists, amantadine derivatives, and MAO-B inhibitors do not appear to affect NORTHERA clearance, and no dose adjustments are required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have been conducted at dosages up to 1,000 mg/kg/day in mice and up to 100 mg/kg/day in rats with no indication of carcinogenic effects. Based on dose per unit body surface area, these two doses correspond to approximately 3 and 0.5 times, respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient. Droxidopa was clastogenic in Chinese hamster ovary cells (chromosome aberration assay), but was not mutagenic in bacteria (Ames assay), and was not clastogenic in a mouse micronucleus assay.

Studies in rats show that droxidopa has no effect on fertility.

13.2 Animal Toxicology and Pharmacology

Rats and mice treated for 52 and 80 weeks, respectively, at doses similar to human doses (100 to 300 mg/kg/day for rats and 300 to 1,000 mg/kg/day for mice) had increased incidences of renal and cardiac lesions (rats and mice) and deaths (rats only). No signs of toxicity were observed in monkeys or dogs given droxidopa for 13 weeks at doses 32 times (3,000 mg/kg/day) and 37 times (2,000 mg/kg/day), respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient, when based on body surface area.

14 CLINICAL STUDIES

14.1 Studies in Neurogenic Orthostatic Hypotension

Clinical studies (described below) examined the efficacy of NORTHERA in the short-term (1 to 2 weeks) and over longer-term periods (8 weeks; 3 months). Studies 301 and 306B showed a treatment effect of NORTHERA at Week 1, but none of the studies demonstrated continued efficacy beyond 2 weeks of treatment.

Study 306B was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study in patients with symptomatic NOH and Parkinson's disease. Patients entering the study were required to have a decrease of at least 20 mm Hg or 10 mm Hg, respectively, in systolic or diastolic blood pressure, within 3 minutes

after standing, as well as symptoms associated with neurogenic orthostatic hypotension. The study had an initial dose titration period that lasted up to 2 weeks in which patients received placebo or 100 to 600 mg of NORTHERA three times daily, followed by an 8-week treatment period.

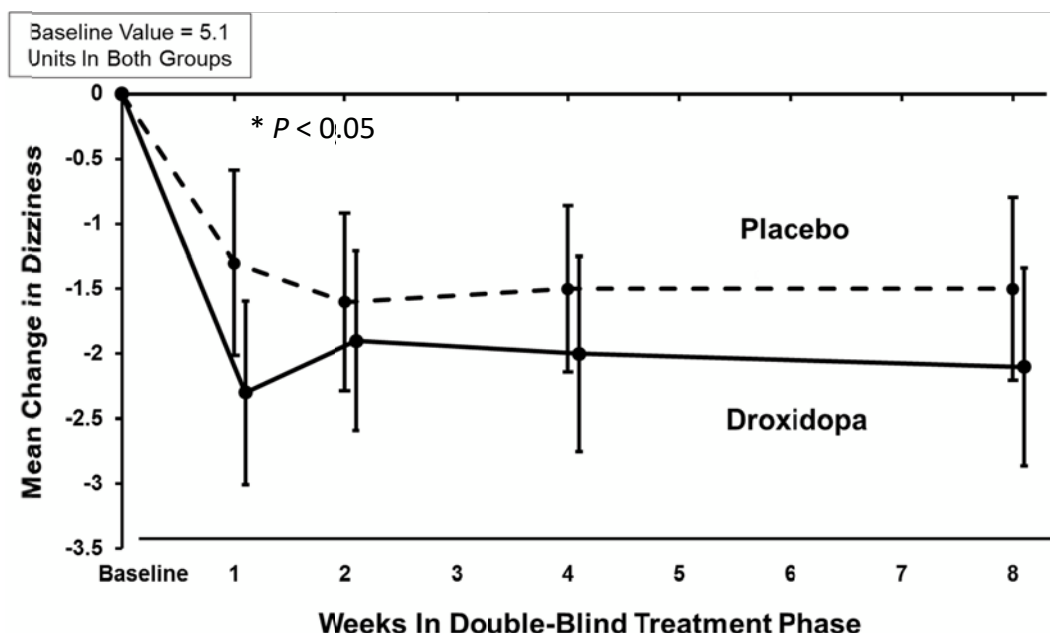
Efficacy was measured using the OHSA Item #1 score (“dizziness, lightheadedness, feeling faint, and feeling like you might black out”) at Week 1, in patients who had completed titration and 1 week of maintenance therapy.

A total of 171 patients were enrolled, and 147 patients were included in the efficacy analysis. The mean age was 72 years, and patients were mostly Caucasian. During the study, 94% of placebo-treated patients and 88% on NORTHERA were taking dopa-decarboxylase inhibitors; 17% of placebo-treated patients and 26% on NORTHERA were taking fludrocortisone. There were more premature discontinuations in the NORTHERA group (28%) than in the placebo group (20%).

In both groups, the mean baseline dizziness score was 5.1 on an 11-point scale. At Week 1, patients showed a statistically significant mean 0.9-unit decrease in dizziness with NORTHERA versus placebo ($P=0.028$), but the effect did not persist beyond Week 1. The data at all time points are shown in Figure 1.

Patients receiving NORTHERA also had a greater increase, compared to placebo, in the Week 1 lowest standing systolic blood pressure within 3 minutes after standing (5.6 mm Hg; $P=0.032$).

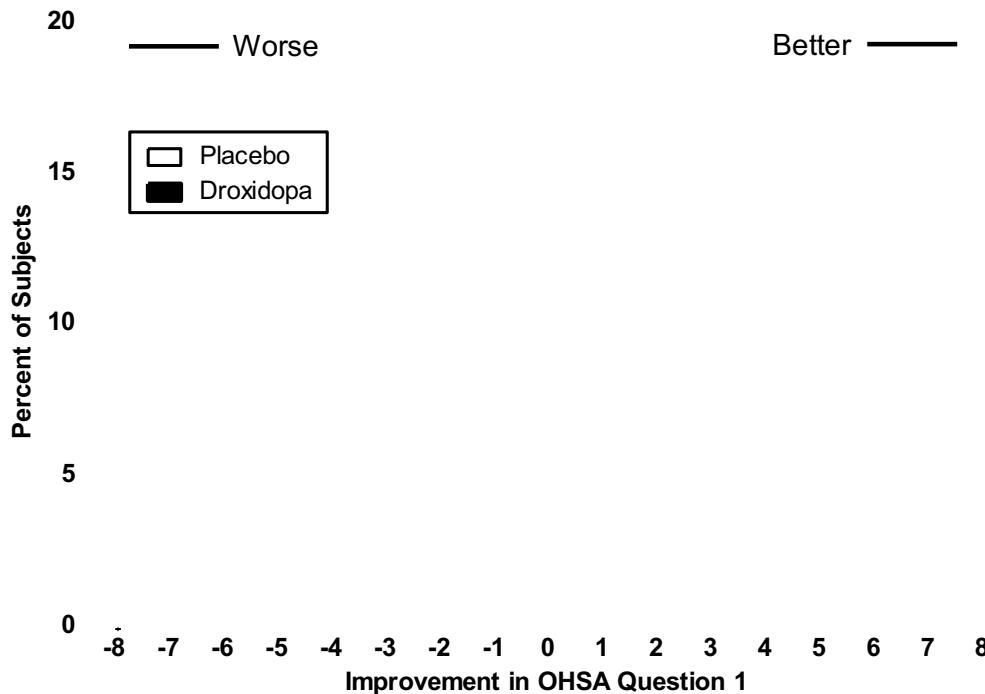
Figure 1. Mean Change in OHSA Item 1 Score by Week in Study 306B



Note: The graph is based on observed data only. The error bars are the 95% confidence interval of the mean change from baseline in OHSA Item 1 scores.

Figure 2. Distribution of Patients by Change in OHSA Item 1, Baseline to Week 1, in Study 306B

Figure 2 shows the distribution of changes from Baseline to Week 1 in the OHSA Item #1 score. Overall, the figure shows that patients treated with NORTHERA improved more than those treated with placebo.



Study 301 was a multicenter, multinational, double-blind, randomized, placebo- controlled, parallel-group study in patients with symptomatic neurogenic orthostatic hypotension. The study included an initial open-label dose titration period, a 7-day wash-out period, and a randomized double-blind 7-day treatment period. To be eligible for enrollment, patients were required to have a decrease in systolic or diastolic blood pressure of at least 20 or 10 mm Hg, respectively, within 3 minutes after standing. The study was enriched, such that only patients who had been identified as ‘responders’ during the titration period were randomized to NORTHERA or placebo. To be considered a responder, a patient had to demonstrate improvement on the OHSA Item #1 score by at least 1 point, as well as an increase in systolic blood pressure of at least 10 mm Hg post-standing, during the open-label dose titration period. Patients who dropped out during the titration period because of side effects or other reasons were also not included in the double-blind portion of the study.

Patients had a primary diagnosis of Parkinson’s disease (n=60), pure autonomic failure (n=36), or multiple system atrophy (n=26). The mean age was 60 years, and most were Caucasian. 45% of patients were taking dopa-decarboxylase inhibitors, and 29% were taking fludrocortisone.

Efficacy was measured using the Orthostatic Hypotension Questionnaire (OHQ), a patient-reported outcome that measures symptoms of NOH and their impact on the patient's ability to perform daily activities that require standing and walking. The OHQ includes OHSA Item #1 as one of several components. A statistically significant treatment effect was not demonstrated on OHQ (treatment effect of 0.4 unit, $P=0.19$).

The mean baseline dizziness score on OHSA Item #1 ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") was 5.2 units on an 11-point scale. At Week 1 of treatment, patients showed a mean 0.7-unit decrease in dizziness with NORTHERA versus placebo ($P=0.06$).

Study 302 (n=101) was a placebo-controlled, 2-week randomized withdrawal study of NORTHERA in patients with symptomatic NOH. Study 303 (n=75) was an extension of Studies 301 and 302, where patients received their titrated dose of NORTHERA for 3 months and then entered a 2-week randomized withdrawal phase. Neither study showed a statistically significant difference between treatment arms on its primary endpoint. Considering these data, the effectiveness of NORTHERA beyond 2 weeks is uncertain, and patients should be evaluated periodically to determine whether NORTHERA is continuing to provide a benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NORTHERA capsules are supplied in the following dosage strengths:

100 mg: Hard gelatin, size 3 capsule, with an opaque light blue cap and an opaque white body, printed with "Northera" on body and "100" on cap, filled with a white to light brown powder.

200 mg: Hard gelatin, size 2 capsule, with an opaque light yellow cap and an opaque white body, printed with "Northera" on body and "200" on cap, filled with a white to light brown powder.

300 mg: Hard gelatin, size 1 capsule, with an opaque light green cap and an opaque white body, printed with "Northera" on body and "300" on cap, filled with a white to light brown powder.

100 mg 90-count bottle (NDC code# 67386-820-19)

200 mg 90-count bottle (NDC code# 67386-821-19)

300 mg 90-count bottle (NDC code# 67386-822-19)

16.2 Storage and Handling

NORTHERA capsules should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION Eleva-

tions in Blood Pressure

Counsel patients that NORTHERA causes elevations in blood pressure and increases the risk of supine hypertension, which could lead to strokes, heart attacks, and death. Instruct patients to rest and sleep in an upper-body elevated position and monitor blood pressure. Instruct patients how to manage observed blood pressure elevations. To reduce the risk of supine hypertension, in addition to raising the upper body, the late afternoon dose of NORTHERA should be taken at least three hours before bedtime.

Concomitant Treatments

Counsel patients about the concomitant use of drugs to treat other conditions that may have an additive effect with NORTHERA [see *Drug Interactions (7)*].

Pregnancy

Counsel patients to consult a physician if they are nursing, pregnant, or planning to become pregnant while taking NORTHERA.

Food

Patients should take NORTHERA the same way each time, either with food or without food.

Missed Dose

If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose.

Manufactured for: Lundbeck
Deerfield, IL 60015, U.S.A.



TM of Lundbeck NA Ltd.

APPENDIX B

Carbidopa Prescribing Information

LODOSYN[®]

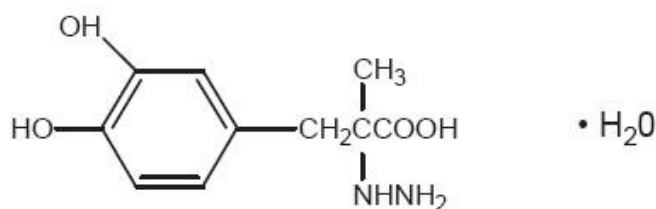
(CARBIDOPA)

TABLETS

When LODOSYN (Carbidopa) is to be given to carbidopa-naïve patients who are being treated with levodopa, the two drugs should be given at the same time, starting with no more than 20 to 25% of the previous daily dosage of levodopa when given without LODOSYN (Carbidopa). At least twelve hours should elapse between the last dose of levodopa and initiation of therapy with LODOSYN (Carbidopa) and levodopa. See the **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections before initiating therapy.

DESCRIPTION

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (–)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is C₁₀H₁₄N₂O₄•H₂O and its structural formula is:



LODOSYN (Carbidopa) tablets contain 25 mg of carbidopa. Inactive ingredients are cellulose, FD&C Yellow 6, magnesium stearate and starch.

Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its

characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.

Mechanism of Action

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier.

However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Pharmacodynamics

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

The incidence of levodopa-induced nausea and vomiting is less when LODOSYN is used with levodopa than when levodopa is used without LODOSYN. In many patients, this reduction in nausea and vomiting will permit more rapid dosage titration.

Carbidopa inhibits decarboxylation of peripheral levodopa. Carbidopa has not been demonstrated to have any overt pharmacodynamic actions in the recommended doses. It does not appear to cross the blood-brain barrier readily and does not affect the metabolism of levodopa within the central nervous system at doses of carbidopa that are recommended for maximum effective inhibition of peripheral decarboxylation of levodopa.

Since its decarboxylase-inhibiting activity is limited primarily to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. However, since levodopa and carbidopa compete with certain amino acids for transport across the gut wall, the absorption of levodopa and carbidopa may be impaired in some patients on a high protein diet.

Pharmacokinetics

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

In clinical pharmacologic studies, simultaneous administration of separate tablets of

carbidopa and levodopa produced greater urinary excretion of levodopa in proportion to the excretion of dopamine when compared to the two drugs administered at separate times.

Supplemental pyridoxine (vitamin B₆) can be given to patients when they are receiving LODOSYN and levodopa concomitantly or the fixed combination carbidopa-levodopa or carbidopa-levodopa extended release. Previous reports in the medical literature cautioned that high doses of vitamin B₆ should not be taken by patients on levodopa therapy alone because exogenously administered pyridoxine would enhance the metabolism of levodopa to dopamine. The introduction of carbidopa to levodopa therapy, which inhibits the peripheral decarboxylation of levodopa to dopamine, counteracts the metabolic-enhancing effect of pyridoxine.

Carbidopa is combined with levodopa in carbidopa-levodopa and carbidopa-levodopa extended release tablets.

INDICATIONS AND USAGE

LODOSYN is indicated for use with carbidopa-levodopa or with levodopa in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism, which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

LODOSYN is for use with carbidopa-levodopa in patients for whom the dosage of carbidopa-levodopa provides less than adequate daily dosage (usually 70 mg daily) of carbidopa.

LODOSYN is for use with levodopa in the occasional patient whose dosage requirement of carbidopa and levodopa necessitates separate titration of each medication.

LODOSYN is used with carbidopa-levodopa or with levodopa to permit the administration of lower doses of levodopa with reduced nausea and vomiting, more rapid dosage titration, and with a somewhat smoother response. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from the addition of carbidopa.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, supplemental pyridoxine (vitamin B₆), can be given to patients when they are receiving carbidopa and levodopa concomitantly or as carbidopa-levodopa.

Although the administration of LODOSYN permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that

this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa.

Certain patients who responded poorly to levodopa alone have improved when carbidopa and levodopa were given concurrently. This was most likely due to decreased peripheral decarboxylation of levodopa rather than to a primary effect of carbidopa on the peripheral nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa.

In deciding whether to give LODOSYN with carbidopa-levodopa or with levodopa to patients who have nausea and/or vomiting, the physician should be aware that, while many patients may be expected to improve, some may not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing carbidopa and levodopa with levodopa alone, about half the patients with nausea and/or vomiting on levodopa alone improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS

LODOSYN is contraindicated in patients with known hypersensitivity to any component of this drug.

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with levodopa or carbidopa-levodopa combination products with or without LODOSYN. These inhibitors must be discontinued at least two weeks prior to initiating therapy with levodopa. Carbidopa-levodopa or levodopa may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (see **PRECAUTIONS, Drug Interactions**).

Levodopa or carbidopa-levodopa products, with or without LODOSYN, are contraindicated in patients with narrow-angle glaucoma.

WARNINGS

LODOSYN (Carbidopa) has no antiparkinsonian effect when given alone. It is indicated for use with carbidopa-levodopa or levodopa. LODOSYN (Carbidopa) does not decrease adverse reactions due to central effects of levodopa.

When LODOSYN (Carbidopa) is to be given to carbidopa-naïve patients who are being treated with levodopa alone, the two drugs should be given at the same time.

At least twelve hours should elapse between the last dose of levodopa and initiation of therapy with LODOSYN (Carbidopa) and levodopa in combination. Start with no more than one-fifth (20%) to one-fourth (25%) of the previous daily dosage of levodopa when given without LODOSYN (Carbidopa). See the DOSAGE AND ADMINISTRATION section before initiating therapy.

The addition of LODOSYN with levodopa or carbidopa-levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, LODOSYN does not decrease the adverse reactions due to the central effects of levodopa. Because LODOSYN permits more levodopa to reach the brain and more dopamine to be formed, certain adverse central nervous system (CNS) effects, e.g., dyskinesias (involuntary movements), may occur at lower dosages and sooner with levodopa in combination with LODOSYN than with levodopa alone.

Falling Asleep During Activities of Daily Living and Somnolence

Patients taking carbidopa-levodopa products alone or with other dopaminergic drugs have reported suddenly falling asleep without prior warning of sleepiness while engaged in activities of daily living (includes operation of motor vehicles). Some of these episodes resulted in automobile accidents. Although many of these patients reported somnolence while on dopaminergic medications, some did perceive that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some patients reported these events one year after the initiation of treatment.

Falling asleep while engaged in activities of daily living usually occurs in patients experiencing pre-existing somnolence, although some patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness especially since some of the events occur after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients who have already experienced somnolence or an episode of sudden sleep onset should not participate in these activities during treatment with LODOSYN when taking it with other carbidopa-levodopa products.

Before initiating treatment with LODOSYN, advise patients about the potential to develop drowsiness and ask specifically about factors that may increase the risk for somnolence with LODOSYN such as the use of concomitant sedating medications and the presence of sleep disorders. Consider discontinuing LODOSYN in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.). If treatment with LODOSYN continues, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hyperpyrexia and Confusion:

Sporadic cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in association with dose reductions or withdrawal of certain antiparkinsonian agents such as levodopa, carbidopa-levodopa, or carbidopa-levodopa extended-release. Therefore, patients should be observed carefully when the dosage of levodopa or carbidopa-levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin, have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential

diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS; however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

General

As with levodopa alone, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended concomitant therapy with LODOSYN and levodopa, or with LODOSYN and carbidopa-levodopa or any combination of these drugs.

Impulse Control/Compulsive Behaviors

Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, binge eating, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are used for the treatment of Parkinson's disease and that increase central dopaminergic tone, including Lodosyn taken with levodopa and carbidopa. In some cases, although not all, these urges were reported to have stopped when the dose of anti-Parkinson medications was reduced or discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Lodosyn. Physicians should consider dose reduction or stopping Lodosyn or levodopa if a patient develops such urges while taking Lodosyn with carbidopa/levodopa.

Hallucinations/Psychotic-Like Behavior

Hallucinations and psychotic like behavior have been reported with dopaminergic medications. In general, hallucinations present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Hallucinations may be accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming. LODOSYN when taken with carbidopa-levodopa may have similar effects on thinking and behavior. This abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Ordinarily, patients with a major psychotic disorder should not be treated with LODOSYN and carbidopa-levodopa, because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of LODOSYN.

Dyskinesia

LODOSYN (Carbidopa) may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia.

Depression

Patients treated with LODOSYN and carbidopa-levodopa should be observed carefully for the development of depression with concomitant suicidal tendencies.

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using LODOSYN tablets for Parkinson's disease.

Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Information for Patients

It is important that LODOSYN with levodopa be taken at regular intervals according to the schedule outlined by the health care provider. Caution patients not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations without first consulting a physician.

Advise patients that sometimes a ‘wearing-off’ effect may occur at the end of the dosing interval. Tell patients to notify the prescriber if such response poses a problem to lifestyle.

Patients should be advised that occasionally dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of LODOSYN and levodopa. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying thus delaying the absorption of levodopa. Iron salts (such as in multivitamin tablets) may also reduce the amount of levodopa available in the body. The above factors may reduce the clinical effectiveness of the LODOSYN and levodopa therapy.

Alert patients to the possibility of sudden onset of sleep during daily activities, in some cases without awareness or warning signs, when they are taking dopaminergic agents, including levodopa. Advise patients to exercise caution while driving or operating machinery and that if they have experience somnolence and/or sudden sleep onset, they must refrain from these activities. (See WARNINGS, Falling Asleep During Activities of Daily Living and Somnolence General.)

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment

of Parkinson's disease, including LODOSYN and levodopa. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges, or other intense urges while taking LODOSYN and levodopa. Physicians should consider dose reduction or stopping Lodosyn and levodopa if a patient develops such urges while taking Lodosyn with carbidopa/levodopa (See PRECAUTIONS, Impulse Control/Compulsive Behaviors).

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during concomitant administration of carbidopa and levodopa than with levodopa alone.

Levodopa and carbidopa-levodopa combination products may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with LODOSYN (Carbidopa) given with levodopa or carbidopa-levodopa fixed dose combination products.

Symptomatic postural hypotension has occurred when LODOSYN, given with levodopa or carbidopa-levodopa combination products, was added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with LODOSYN, given with or without levodopa or carbidopa-levodopa combination products, is started, dosage adjustment of the antihypertensive drug may be required.

For patients receiving monoamine oxidase inhibitors (Type A or B), see **CONTRAINDICATIONS**. Concomitant therapy with selegiline or rasagiline and LODOSYN and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see **CONTRAINDICATIONS**).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Dopamine D₂ receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with LODOSYN and levodopa or carbidopa-levodopa combination products should be carefully observed for loss of therapeutic response

LODOSYN and iron salts or multi vitamins containing iron salts should be co administered with caution. Iron salts can form chelates with levodopa and carbidopa and consequently reduce the bioavailability of carbidopa and levodopa.

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There were no significant differences between treated and control rats with respect to mortality or neoplasia in a 96-week study of carbidopa at oral doses of 25, 45, or 135 mg/kg/day. Combinations of carbidopa and levodopa (10-20, 10-50, 10-100 mg/kg/day) were given orally to rats for 106 weeks. No effect on mortality or incidence and type of neoplasia was seen when compared to concurrent controls.

Mutagenesis

Mutagenicity studies have not been performed with either carbidopa or the combination of carbidopa and levodopa.

Fertility

Carbidopa had no effect on the mating performance, fertility, or survival of the young when administered orally to rats at doses of 30, 60, or 120 mg/kg/day. The highest dose caused a moderate decrease in body weight gain in males.

The administration of carbidopa-levodopa at dose levels of 10-20, 10-50, or 10-100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the growth and survival of the young.

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies with LODOSYN in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. LODOSYN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Carbidopa, at doses as high as 120 mg/kg/day, was without teratogenic effects in the mouse or rabbit. In the rabbit, but not in the mouse, carbidopa-levodopa produced visceral anomalies, similar to those seen with levodopa alone, at approximately 7 times the maximum recommended human dose. The teratogenic effect of levodopa in rabbits was unchanged by the concomitant administration of carbidopa.

Nursing Mothers

It is not known whether carbidopa is excreted in human milk. Because many drugs are excreted in human milk, and because of their potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established, and use of the drug in patients below the age of 18 is not recommended.

Geriatric Use

Clinical studies of LODOSYN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease and other drug therapy.

ADVERSE REACTIONS

Carbidopa has not been demonstrated to have any overt pharmacodynamic actions in the recommended doses. The only adverse reactions that have been observed have been with concomitant use of carbidopa with other drugs such as levodopa, and with carbidopa-levodopa combination products.

When LODOSYN is administered concomitantly with levodopa or carbidopa-levodopa combination products, the most common adverse reactions have included dyskinesias such as choreiform, dystonic, and other involuntary movements, and nausea. Other adverse reactions reported with LODOSYN when administered concomitantly with levodopa alone or carbidopa-levodopa combination products were psychotic episodes including delusions, hallucinations, and paranoid ideation, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with concomitant use of LODOSYN and levodopa has not been established.

The following other adverse reactions have been reported with levodopa and carbidopa-levodopa combination products. These same adverse reactions may also occur when LODOSYN is administered with these products.

Body as a Whole: abdominal pain and distress, asthenia, chest pain, fatigue.

Cardiovascular: cardiac irregularities, hypertension, myocardial infarction, hypotension including orthostatic hypotension, palpitation, phlebitis, syncope.

Gastrointestinal: anorexia, bruxism, burning sensation of the tongue, constipation, dark saliva, development of duodenal ulcer, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, gastrointestinal bleeding, gastrointestinal pain, heartburn, hiccups, sialorrhea, taste alterations, vomiting.

Hematologic: hemolytic and non-hemolytic anemia, leukopenia, thrombocytopenia, agranulocytosis.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura, bullous lesions (including pemphigus-like reactions).

Metabolic: edema, weight gain, weight loss.

Musculoskeletal: back pain, leg pain, muscle cramps, shoulder pain.

Nervous System/Psychiatric: Psychotic episodes including delusions, hallucinations and paranoid ideation, neuroleptic malignant syndrome (NMS, see WARNINGS), bradykinetic episodes (“on-off” phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms. Convulsions also have occurred; however, a causal relationship with LODOSYN and levodopa, has not been established.

Respiratory: upper respiratory infection, dyspnea, pharyngeal pain, cough.

Skin: flushing, increased sweating, malignant melanoma (see also **CONTRAINDICATIONS**), rash, alopecia, dark sweat.

Special Senses: oculogyric crises, diplopia, blurred vision, dilated pupils.

Urogenital: dark urine, priapism, urinary frequency, urinary incontinence, urinary retention, urinary tract infection.

Laboratory Tests: abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs test; elevated serum glucose; decreased hemoglobin and hematocrit; decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; white blood cells, bacteria and blood in the urine; protein and glucose in the urine.

Miscellaneous: bizarre breathing patterns, faintness, hoarseness, hot flashes, malaise, neuroleptic malignant syndrome, sense of stimulation.

OVERDOSAGE

No reports of overdose with LODOSYN have been received. Management of overdosage with carbidopa is the same as that with levodopa or carbidopa-levodopa preparations.

In the event of overdosage, general supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously, and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as LODOSYN should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known. Pyridoxine is not effective in reversing the actions of LODOSYN.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION

Whether given with carbidopa-levodopa or with levodopa, the optimal daily dose of LODOSYN must be determined by careful titration. Most patients respond to a 1:10 proportion of carbidopa and levodopa, provided the daily dosage of carbidopa is 70 mg or more a day. The maximum daily dosage of carbidopa should not exceed 200 mg, since clinical experience with larger dosages is limited. If the patient is taking carbidopa-levodopa, the amount of carbidopa in carbidopa-levodopa should be considered when calculating the total amount of LODOSYN to be administered each day.

Patients Receiving Carbidopa-Levodopa Who Require Additional Carbidopa

Some patients taking carbidopa-levodopa may not have adequate reduction in nausea and vomiting when the dosage of carbidopa is less than 70 mg a day, and the dosage of levodopa is less than 700 mg a day. When these patients are taking carbidopa-levodopa, 25 mg of LODOSYN may be given with the first dose of carbidopa-levodopa each day. Additional doses of 12.5 mg or 25 mg may be given during the day with each dose of carbidopa-levodopa. LODOSYN may be given with any dose carbidopa-levodopa as required for optimum therapeutic response. The maximum daily dosage of carbidopa, given as LODOSYN and as carbidopa-levodopa, should not exceed 200 mg.

Patients Requiring Individual Titration of Carbidopa and

Levodopa Dosage

Although carbidopa-levodopa is the most frequently used of carbidopa and levodopa administration, there may be an occasional patient who requires individually titrated doses of these two drugs. **In these patients, LODOSYN (carbidopa) should be initiated at a dosage of 25 mg three or four times a day. The two drugs should be given at the same time, starting with no more than one-fifth (20%) to one-fourth (25%) of the previous or recommended daily dosage of levodopa when given without LODOSYN (Carbidopa). In patients already receiving levodopa therapy, at least twelve hours should elapse between the last dose of levodopa and initiation of therapy with LODOSYN (Carbidopa) and levodopa. A convenient way to initiate therapy in these patients is in the morning following a night when the patient has not taken levodopa for at least twelve hours.** Health care providers who prescribe separate doses of LODOSYN and levodopa should be thoroughly familiar with the directions for use of each drug.

Dosage Adjustment

Dosage of LODOSYN may be adjusted by adding or omitting one-half or one tablet a day. Because both therapeutic and adverse responses occur more rapidly with combined therapy than when only levodopa is given, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly when LODOSYN and levodopa are given concomitantly than when levodopa is given without LODOSYN. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Current evidence indicates other standard antiparkinsonian drugs may be continued while carbidopa and levodopa are being administered. However, the dosage of such other standard antiparkinsonian drugs may require adjustment.

Interruption of Therapy

Sporadic cases of hyperpyrexia and confusion have been associated with dose reductions and withdrawal of carbidopa-Levodopa) or carbidopa-levodopa Extended Release. Patients should be observed carefully if abrupt reduction or discontinuation of carbidopa-levodopa or carbidopa-levodopa Extended-Release is required, especially if the patient is receiving neuroleptics. (See WARNINGS.)

If general anesthesia is required, therapy may be continued as long as the patient is

permitted to take fluids and medication by mouth. When therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be resumed as soon as the patient is able to take medication orally.

HOW SUPPLIED

Tablets LODOSYN, 25 mg, are orange, round, compressed tablets that are scored and coded

711 on one side and LODOSYN on the other.

They are supplied as follows:

NDC 0056-0511-68 bottles of 100.

Storage

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F).

Manufactured in Canada by:

Valeant Pharmaceuticals International, Inc.
Steinbach, MB R5G 1Z7

Manufactured for:

Valeant Pharmaceuticals North America LLC
Bridgewater, NJ

08807 USA Rev.

2/2014

APPENDIX C

UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
 - Muscular rigidity
 - 4-6 Hz rest tremor
 - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

APPENDIX D
Unified Parkinson's Disease Rating Scale (UPDRS) Parts 2 and 3

Unified Parkinson's Disease Rating Scale Part 2

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech

- 0 = Normal.
- 1 = Mildly affected. No difficulty being understood.
- 2 = Moderately affected. Sometimes asked to repeat statements.
- 3 = Severely affected. Frequently asked to repeat statements.
- 4 = Unintelligible most of the time.

6. Salivation

- 0 = Normal.
- 1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
- 2 = Moderately excessive saliva; may have minimal drooling.
- 3 = Marked excess of saliva with some drooling.
- 4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

- 0 = Normal.
- 1 = Rare choking.
- 2 = Occasional choking.
- 3 = Requires soft food.
- 4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

- 0 = Normal.
- 1 = Slightly slow or small.
- 2 = Moderately slow or small; all words are legible.
- 3 = Severely affected; not all words are legible.
- 4 = The majority of words are not legible.

9. Cutting food and handling utensils

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can cut most foods, although clumsy and slow; some help needed.
- 3 = Food must be cut by someone, but can still feed slowly.
- 4 = Needs to be fed.

10. Dressing

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Occasional assistance with buttoning, getting arms in sleeves.
- 3 = Considerable help required, but can do some things alone.
- 4 = Helpless.

11. Hygiene

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Needs help to shower or bathe; or very slow in hygienic care.
- 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
- 4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can turn alone or adjust sheets, but with great difficulty.
- 3 = Can initiate, but not turn or adjust sheets alone.
- 4 = Helpless.

13. Falling (unrelated to freezing)

- 0 = None.
- 1 = Rare falling.
- 2 = Occasionally falls, less than once per day.
- 3 = Falls an average of once daily.
- 4 = Falls more than once daily.

Unified Parkinson's Disease Rating Scale Part 2 (Continued)

14. Freezing when walking

0 = None.

1 = Rare freezing when walking; may have start hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking

0 = Normal.

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

0 = Absent.

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

0 = None.

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching; not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

Unified Parkinson's Disease Rating Scale Part 3

III. MOTOR EXAMINATION

18. Speech

- 0 = Normal.
- 1 = Slight loss of expression, diction and/or volume.
- 2 = Monotone, slurred but understandable; moderately impaired.
- 3 = Marked impairment, difficult to understand.
- 4 = Unintelligible.

19. Facial Expression

- 0 = Normal.
- 1 = Minimal hypomimia, could be normal "Poker Face".
- 2 = Slight but definitely abnormal diminution of facial expression
- 3 = Moderate hypomimia; lips parted some of the time.
- 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
- 3 = Moderate in amplitude and present most of the time.
- 4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

- 0 = Absent.
- 1 = Slight; present with action.
- 2 = Moderate in amplitude, present with action.
- 3 = Moderate in amplitude with posture holding as well as action.
- 4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

- 0 = Absent.
- 1 = Slight or detectable only when activated by mirror or other movements.
- 2 = Mild to moderate.
- 3 = Marked, but full range of motion easily achieved.
- 4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

Unified Parkinson's Disease Rating Scale Part 3 (Continued)

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

- 0 = Normal.
- 1 = Slow; or may need more than one attempt.
- 2 = Pushes self up from arms of seat.
- 3 = Tends to fall back and may have to try more than one time, but can get up without help.
- 4 = Unable to arise without help.

28. Posture

- 0 = Normal erect.
- 1 = Not quite erect, slightly stooped posture; could be normal for older person.
- 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
- 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
- 4 = Marked flexion with extreme abnormality of posture.

29. Gait

- 0 = Normal.
- 1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
- 2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
- 3 = Severe disturbance of gait, requiring assistance.
- 4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

- 0 = Normal.
- 1 = Retropulsion, but recovers unaided.
- 2 = Absence of postural response; would fall if not caught by examiner.
- 3 = Very unstable, tends to lose balance spontaneously.
- 4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

- 0 = None.
- 1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
- 2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
- 3 = Moderate slowness, poverty or small amplitude of movement.
- 4 = Marked slowness, poverty or small amplitude of movement.

APPENDIX E

Hoehn and Yahr Staging

Hoehn and Yahr Staging

(Select only from among options below)

- Stage 0.0 = Asymptomatic.
- Stage 1.0 = Unilateral involvement only.
- Stage 1.5 = Unilateral and axial involvement.
- Stage 2.0 = Bilateral involvement without impairment of balance.
- Stage 2.5 = Mild bilateral involvement with recovery on retropulsion (pull) test without rater assistance.
- Stage 3.0 = Mild to moderate bilateral involvement; some postural instability but physically independent; needs assistance to recover from pull test.
- Stage 4.0 = Severe disability; still able to walk or stand unassisted.
- Stage 5.0 = Wheelchair bound or bedridden unless aided.

Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. *Neurology* 1967, 17:427-442.

APPENDIX F:
Montreal Cognitive Assessment (MoCA)
Versions 7.1 (Original), 7.2 (Alternate), and 7.3 (Alternate)
Samples provided in this appendix are for reference only.

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :

Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE		Copy cube		Draw CLOCK (Ten past eleven) (3 points)		POINTS
						___/5
		[]	[]	[]	[]	
		Contour	Numbers	Hands		
NAMING						
						___/3
		[]	[]	[]		
MEMORY		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.				
		FACE	VELVET	CHURCH	DAISY	RED
1st trial						
2nd trial						
		No points				
ATTENTION		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4				
		Subject has to repeat them in the backward order [] 7 4 2				
		___/2				
		Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors				
		[] FBACMNAAJKLBAFAKDEAAAJAMOFAAB				
		___/1				
		Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65				
		4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt				
		___/3				
LANGUAGE		Repeat : I only know that John is the one to help today. []				
		The cat always hid under the couch when dogs were in the room. []				
		___/2				
		Fluency / Name maximum number of words in one minute that begin with the letter F [] ____ (N ≥ 11 words)				
		___/1				
ABSTRACTION		Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler				
		___/2				
DELAYED RECALL		Has to recall words WITH NO CUE				
		FACE	VELVET	CHURCH	DAISY	RED
		[]	[]	[]	[]	[]
		Points for UNCUE recall only				
Optional		Category cue				
		Multiple choice cue				
		___/5				
ORIENTATION		[] Date [] Month [] Year [] Day [] Place [] City				
		___/6				
© Z.Nasreddine MD		www.mocatest.org		Normal ≥ 26 / 30		TOTAL
Administered by: _____						___/30
				Add 1 point if ≤ 12 yr edu		

Date of birth :
DATE :

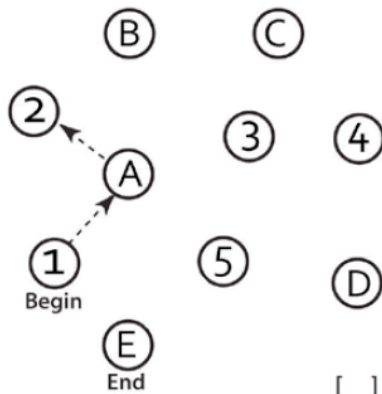
VISUOSPATIAL / EXECUTIVE							POINTS																		
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>Begin</p> <p>End</p> </div> <div style="text-align: center;"> <p>Copy rectangle</p> </div> </div>				<p>Draw CLOCK (Five past four) (3 points)</p>		<div style="display: flex; justify-content: space-between;"> [] [] [] </div>	<div style="display: flex; justify-content: space-between;"> ___/5 </div>																		
<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>NAMING</p> </div> <div style="text-align: center;"> </div> <div style="text-align: center;"> </div> </div>							<div style="display: flex; justify-content: space-between;"> ___/3 </div>																		
<div style="display: flex;"> <div style="flex: 1;"> <p>MEMORY</p> <p>Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.</p> </div> <table border="1" style="border-collapse: collapse; text-align: center;"> <tr> <td></td> <td>TRUCK</td> <td>BANANA</td> <td>VIOLIN</td> <td>DESK</td> <td>GREEN</td> </tr> <tr> <td>1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table> </div>								TRUCK	BANANA	VIOLIN	DESK	GREEN	1st trial						2nd trial						<div style="display: flex; justify-content: space-between;"> No points </div>
	TRUCK	BANANA	VIOLIN	DESK	GREEN																				
1st trial																									
2nd trial																									
<div style="display: flex;"> <div style="flex: 1;"> <p>ATTENTION</p> <p>Read list of digits (1 digit/ sec.).</p> <p>Subject has to repeat them in the forward order</p> <p>Subject has to repeat them in the backward order</p> </div> <div style="flex: 2;"> <p>[] 3 2 9 6 5</p> <p>[] 8 5 2</p> </div> </div>							<div style="display: flex; justify-content: space-between;"> ___/2 </div>																		
<p>Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors</p> <p>[] FBACMNAAJKLBAFAKDEAAAJAMOF AAB</p>							<div style="display: flex; justify-content: space-between;"> ___/1 </div>																		
<p>Serial 7 subtraction starting at 90</p> <p>[] 83 [] 76 [] 69 [] 62 [] 55</p> <p>4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt</p>							<div style="display: flex; justify-content: space-between;"> ___/3 </div>																		
<p>LANGUAGE</p> <p>Repeat : A bird can fly into closed windows when it's dark and windy. []</p> <p>The caring grandmother sent groceries over a week ago. []</p>							<div style="display: flex; justify-content: space-between;"> ___/2 </div>																		
<p>Fluency / Name maximum number of words in one minute that begin with the letter S</p> <p>[] _____ (N ≥ 11 words)</p>							<div style="display: flex; justify-content: space-between;"> ___/1 </div>																		
<p>ABSTRACTION</p> <p>Similarity between e.g. carrot - potato = vegetable. [] diamond - ruby [] cannon - rifle</p>							<div style="display: flex; justify-content: space-between;"> ___/2 </div>																		
<table border="1" style="border-collapse: collapse; text-align: center;"> <tr> <td rowspan="2" style="width: 20%;">DELAYED RECALL</td> <td>Has to recall words</td> <td>TRUCK</td> <td>BANANA</td> <td>VIOLIN</td> <td>DESK</td> <td>GREEN</td> <td rowspan="2">Points for UNCUEd recall only</td> </tr> <tr> <td>WITH NO CUE</td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> </tr> </table>							DELAYED RECALL	Has to recall words	TRUCK	BANANA	VIOLIN	DESK	GREEN	Points for UNCUEd recall only	WITH NO CUE	[]	[]	[]	[]	[]	<div style="display: flex; justify-content: space-between;"> ___/5 </div>				
DELAYED RECALL	Has to recall words	TRUCK	BANANA	VIOLIN	DESK	GREEN		Points for UNCUEd recall only																	
	WITH NO CUE	[]	[]	[]	[]	[]																			
<p>Optional</p> <table border="1" style="border-collapse: collapse; text-align: center;"> <tr> <td>Category cue</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Multiple choice cue</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>							Category cue						Multiple choice cue						<div style="display: flex; justify-content: space-between;"> ___/5 </div>						
Category cue																									
Multiple choice cue																									
<p>ORIENTATION</p> <p>[] Date [] Month [] Year [] Day [] Place [] City</p>							<div style="display: flex; justify-content: space-between;"> ___/6 </div>																		
<p>Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD</p> <p>© Z.Nasreddine MD www.mocatest.org</p>							<div style="display: flex; justify-content: space-between;"> Normal ≥ 26 / 30 TOTAL ___/30 </div>																		
<p>Administered by:</p>							<div style="display: flex; justify-content: space-between;"> Add 1 point if ≤ 12 yr edu </div>																		

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.3 Alternative Version

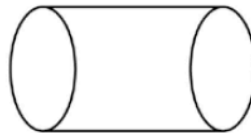
NAME :
Education :
Sex :

Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE



Copy cylinder



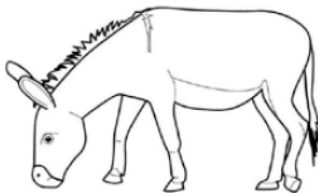
Draw CLOCK (Ten past nine)
(3 points)

[] Contour [] Numbers [] Hands

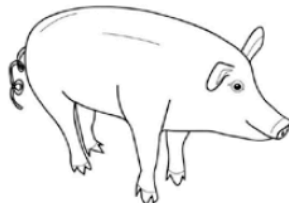
POINTS

___/5

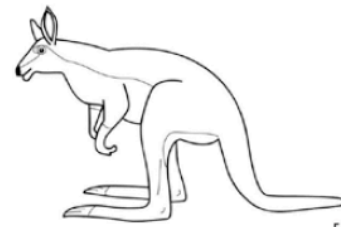
NAMING



[]



[]



[]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

TRAIN

EGG

HAT

CHAIR

BLUE

1st trial

2nd trial

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order

[] 5 4 1 8 7

Subject has to repeat them in the backward order

[] 1 7 4

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[] FBACMNAAJKLBAFAKDEAAAAJAMOF AAB

___/1

Serial 7 subtraction starting at 80

[] 73

[] 66

[] 59

[] 52

[] 45

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

___/3

LANGUAGE

Repeat : She heard his lawyer was the one to sue after the accident. []

The little girls who were given too much candy got stomach aches. []

___/2

Fluency / Name maximum number of words in one minute that begin with the letter B [] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit

[] eye - ear

[] trumpet - piano

___/2

DELAYED RECALL

Has to recall words

TRAIN

EGG

HAT

CHAIR

BLUE

WITH NO CUE

[]

[]

[]

[]

[]

Points for
UNCUED
recall only

___/5

Optional

Category cue

Multiple choice cue

ORIENTATION

[] Date

[] Month

[] Year

[] Day

[] Place

[] City

___/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Normal $\geq 26 / 30$

TOTAL

___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX G
GDS-15 symptoms score

Geriatric Depression Scale (Short Form) (GDS-15)

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

- | | | |
|---|-----|----|
| 1. Are you basically satisfied with your life? | yes | no |
| 2. Have you dropped many of your activities and interests? | yes | no |
| 3. Do you feel that your life is empty? | yes | no |
| 4. Do you often get bored? | yes | no |
| 5. Are you in good spirits most of the time? | yes | no |
| 6. Are you afraid that something bad is going to happen to you? | yes | no |
| 7. Do you feel happy most of the time? | yes | no |
| 8. Do you often feel helpless? | yes | no |
| 9. Do you prefer to stay at home, rather than going out and doing things? | yes | no |
| 10. Do you feel that you have more problems with memory than most? | yes | no |
| 11. Do you think it is wonderful to be alive now? | yes | no |
| 12. Do you feel worthless the way you are now? | yes | no |
| 13. Do you feel full of energy? | yes | no |
| 14. Do you feel that your situation is hopeless? | yes | no |
| 15. Do you think that most people are better off than you are? | yes | no |

Total Score _____

Geriatric Depression Scale (Short Form) (GDS-15) (Continued)

Geriatric Depression Scale (GDS) Scoring Instructions

Instructions: Score 1 point for each bolded answer. A score of 5 or more suggests depression.

- | | | |
|---|-----|-----------|
| 1. Are you basically satisfied with your life? | yes | no |
| 2. Have you dropped many of your activities and interests? | yes | no |
| 3. Do you feel that your life is empty? | yes | no |
| 4. Do you often get bored? | yes | no |
| 5. Are you in good spirits most of the time? | yes | no |
| 6. Are you afraid that something bad is going to happen to you? | yes | no |
| 7. Do you feel happy most of the time? | yes | no |
| 8. Do you often feel helpless? | yes | no |
| 9. Do you prefer to stay at home, rather than going out and doing things? | yes | no |
| 10. Do you feel that you have more problems with memory than most? | yes | no |
| 11. Do you think it is wonderful to be alive now? | yes | no |
| 12. Do you feel worthless the way you are now? | yes | no |
| 13. Do you feel full of energy? | yes | no |
| 14. Do you feel that your situation is hopeless? | yes | no |
| 15. Do you think that most people are better off than you are? | yes | no |

A score of ≥ 5 suggests depression

Total Score _____

Ref. Yes average: The use of Rating Depression Series in the Elderly, in Poon (ed.): Clinical Memory Assessment of Older Adults, American Psychological Association, 1986

APPENDIX H

FrSBe Scale

Patient's name _____ Gender _____ Age _____ Today's date ____/____/____

Patient's education level (check one): ☐ 12 years or less ☐ More than 12 years Date of onset of illness/injury ____/____/____

Rater's name _____ Relationship to patient _____

1 Almost never 2 Seldom 3 Sometimes 4 Frequently 5 Almost always

	Before illness or injury					At the present time				
1. Speaks only when spoken to.	1	2	3	4	5	1	2	3	4	5
2. Is easily angered or irritated; has emotional outbursts without good reason.	1	2	3	4	5	1	2	3	4	5
3. Repeats certain actions or gets stuck on certain ideas.	1	2	3	4	5	1	2	3	4	5
4. Does things impulsively.	1	2	3	4	5	1	2	3	4	5
5. Mixes up a sequence, gets confused when doing several things in a row.	1	2	3	4	5	1	2	3	4	5
6. Laughs or cries too easily.	1	2	3	4	5	1	2	3	4	5
7. Makes the same mistakes over and over, does not learn from past experience.	1	2	3	4	5	1	2	3	4	5
8. Has difficulty starting an activity, lacks initiative, motivation.	1	2	3	4	5	1	2	3	4	5
9. Makes inappropriate sexual comments and advances, is too flirtatious.	1	2	3	4	5	1	2	3	4	5
10. Does or says embarrassing things.	1	2	3	4	5	1	2	3	4	5
11. Neglects personal hygiene.	1	2	3	4	5	1	2	3	4	5
12. Can't sit still, is hyperactive.	1	2	3	4	5	1	2	3	4	5
13. Denies having problems or is unaware of problems or mistakes.	1	2	3	4	5	1	2	3	4	5
14. Sits around doing nothing.	1	2	3	4	5	1	2	3	4	5
15. Is disorganized.	1	2	3	4	5	1	2	3	4	5
16. Loses control of urine or bowels and seems unconcerned.	1	2	3	4	5	1	2	3	4	5
17. Cannot do two things at once (for example, talk and prepare a meal).	1	2	3	4	5	1	2	3	4	5
18. Talks out of turn, interrupts others in conversations.	1	2	3	4	5	1	2	3	4	5
19. Shows poor judgment, is a poor problem solver.	1	2	3	4	5	1	2	3	4	5
20. Makes up fantastic stories when unable to remember something.	1	2	3	4	5	1	2	3	4	5
21. Has lost interest in things that used to be fun or important to him/her.	1	2	3	4	5	1	2	3	4	5
22. Says one thing, then does another thing.	1	2	3	4	5	1	2	3	4	5
23. Starts things but fails to finish them, "peters out."	1	2	3	4	5	1	2	3	4	5
24. Shows little emotion, is unconcerned and unresponsive.	1	2	3	4	5	1	2	3	4	5

FrSBe Scale (cont.)

	1 Almost never	2 Seldom	3 Sometimes	4 Frequently	5 Almost always	Before illness or injury	At the present time
25. Forgets to do things but then remembers when prompted or when it is too late.						1 2 3 4 5	1 2 3 4 5
26. Is inflexible, unable to change routines.						1 2 3 4 5	1 2 3 4 5
27. Gets in trouble with the law or authorities.						1 2 3 4 5	1 2 3 4 5
28. Does risky things just for the heck of it.						1 2 3 4 5	1 2 3 4 5
29. Is slow moving, lacks energy, inactive.						1 2 3 4 5	1 2 3 4 5
30. Is overly silly, has childish sense of humor.						1 2 3 4 5	1 2 3 4 5
31. Complains that food has no taste or smell.						1 2 3 4 5	1 2 3 4 5
32. Swears.						1 2 3 4 5	1 2 3 4 5
Read each of the following items carefully before responding.							
33. Apologizes for misbehavior (for example, apologizes for swearing).						1 2 3 4 5	1 2 3 4 5
34. Pays attention, concentrates even when there are distractions.						1 2 3 4 5	1 2 3 4 5
35. Thinks things through before acting (for example, considers finances before spending money).						1 2 3 4 5	1 2 3 4 5
36. Uses strategies to remember important things (for example, writes notes to self).						1 2 3 4 5	1 2 3 4 5
37. Is able to plan ahead.						1 2 3 4 5	1 2 3 4 5
38. Is interested in sex.						1 2 3 4 5	1 2 3 4 5
39. Cares about his/her appearance (for example, daily grooming).						1 2 3 4 5	1 2 3 4 5
40. Benefits from feedback, accepts constructive criticism from others.						1 2 3 4 5	1 2 3 4 5
41. Gets involved with activities spontaneously (such as hobbies).						1 2 3 4 5	1 2 3 4 5
42. Does things without being requested to do so.						1 2 3 4 5	1 2 3 4 5
43. Is sensitive to the needs of other people.						1 2 3 4 5	1 2 3 4 5
44. Gets along well with others.						1 2 3 4 5	1 2 3 4 5
45. Acts appropriately for his/her age.						1 2 3 4 5	1 2 3 4 5
46. Starts conversations spontaneously.						1 2 3 4 5	1 2 3 4 5

APPENDIX I

Brand Names of Allowed and Disallowed Concomitant Medications

Allowed Concomitant Medications

The following are examples of medications that may be used during droxidopa administration. **This is not an exhaustive list.**

Drug Type/Generic Name

Brand Name Examples

Opiate analgesics

–codeine

–fentanyl

Abstral®

Actiq®

Duragesic®

Fentora®

Lazanda®

Onsolis®

Sublimaze®

–hydrocodone

Anexsia®

Lortab®

Vicodin®

Zydone®

–hydromorphone

Dilaudid®

Exalgo®

–morphine

Astramorph/PF™

Avinza®

DepoDur®

Duramorph

Kadian®

MS Contin®

–oxycodone

Oxecta®

OxyContin®

Percocet®

Percodan®

Roxicet®

Roxicodone®

Tylox

Nonsteroidal antiinflammatory drugs

–aspirin	Advil®
–ibuprofen	Nuprin®
	Aleve®
–naproxen	Anaprox®
	Naproxyn®
–acetaminophen	Tylenol®

Antibiotics***Quinolone antibiotics***

–gatifloxacin	Zymar®
	Zymaxid®
–levofloxacin	Levaquin®
–moxifloxacin	Avelox®
	Vigamox®
–ciprofloxacin	Cipro®

Macrolide antibiotics

–azithromycin	Zithromax®
	Zmax®
–clarithromycin	Biaxin®
–telithromycin	Ketek®

Dopaminergic medications

-ropinirole	Requip®
-pramipexole	Miramax®
-rotigotine	Neupro®
-levodopa	Sinemet®
	Rytary®
	Parcopa®
	Duopa®
-entacapone	Comtan®
-amantadine	

Cough/cold/allergy products containing only the following as active ingredients***Antihistamine***

–azelastine	–cetirizine, levocetirizine
-------------	-----------------------------

- chlorpheniramine
- fexofenadine
- ketotifen
- levocabastine
- loratadine, desloratadine

Mast-cell stabilizer

- cromolyn

Corticosteroid nasal spray

- beclomethasone
- budesonide
- flunisolide
- fluticasone
- mometasone
- triamcinolone

Antitussive

- benzonatate

Expectorant

- guaifenesin

Astelin®

Astepro®

Zyrtec®

Xyzal®

Chlor-Trimeton®

Allegra®

Zaditor®

Livostin®

Claritin®

Clarinex®

Intal®

Gastrocrom®

Opticrom®

Beconase®

Rhinocort®

Nasarel®

Flonase®

VersaMist®

Nasonex®

Nasacort®

Tessalon®

Mucinex®

Disallowed Concomitant Medications

The following are examples of medications that may NOT be used during droxidopa administration. **This is not an exhaustive list.**

Drug Type/Generic Name

- cocaine
- investigational drugs

Brand Name Examples

Medications which increase blood pressure

- norepinephrine
- ephedrine
- dextroamphetamine/amphetamine
- methylphenidate
- midodrine
- fludrocortisone
- triptans

Levophed®

Adderall®
Ritalin®
Concerta®
Amatine®
Apo-Midodrine®
Florinef®
Imitrex®
Zomig®
Amerge®
Maxalt®
Axert®
Relpax®
Frova®

Norepinephrine reuptake inhibitors

- venlafaxine
- desvenlafaxine
- duloxetine
- milnacipran
- atomoxetine

Effexor®
Pristiq®
Cymbalta®
Savella®
Strattera®

Cough medications containing dex-tromethorphan

Promethazine DM®
Robitussin® Peak Cold DM
Triaminic®
Vicks Formula

